Neurology

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References: 1. J. D. Young, Jr., W. S. Kiser and O. C. Beyer, **Antibiotic Med. & Clin. Therapy**, 6:(Suppl. 1), 53, 1959. 2. W. A. Leff, **ibid.**, p. 44. 3. R. E. Bagdon, L. O. Randall and W. A. Leff, **Ann. New York Acad. Sc.**, 82:(Art. 1), 3, 1959. 4. J. C. Elia, **ibid.**, p. 52.

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1. Wein, A.B.: Clin. Med. 6:44 (Jan.) 1959.
2. Vazuka, F.A.: Neurology 8:446 (June) 1958.

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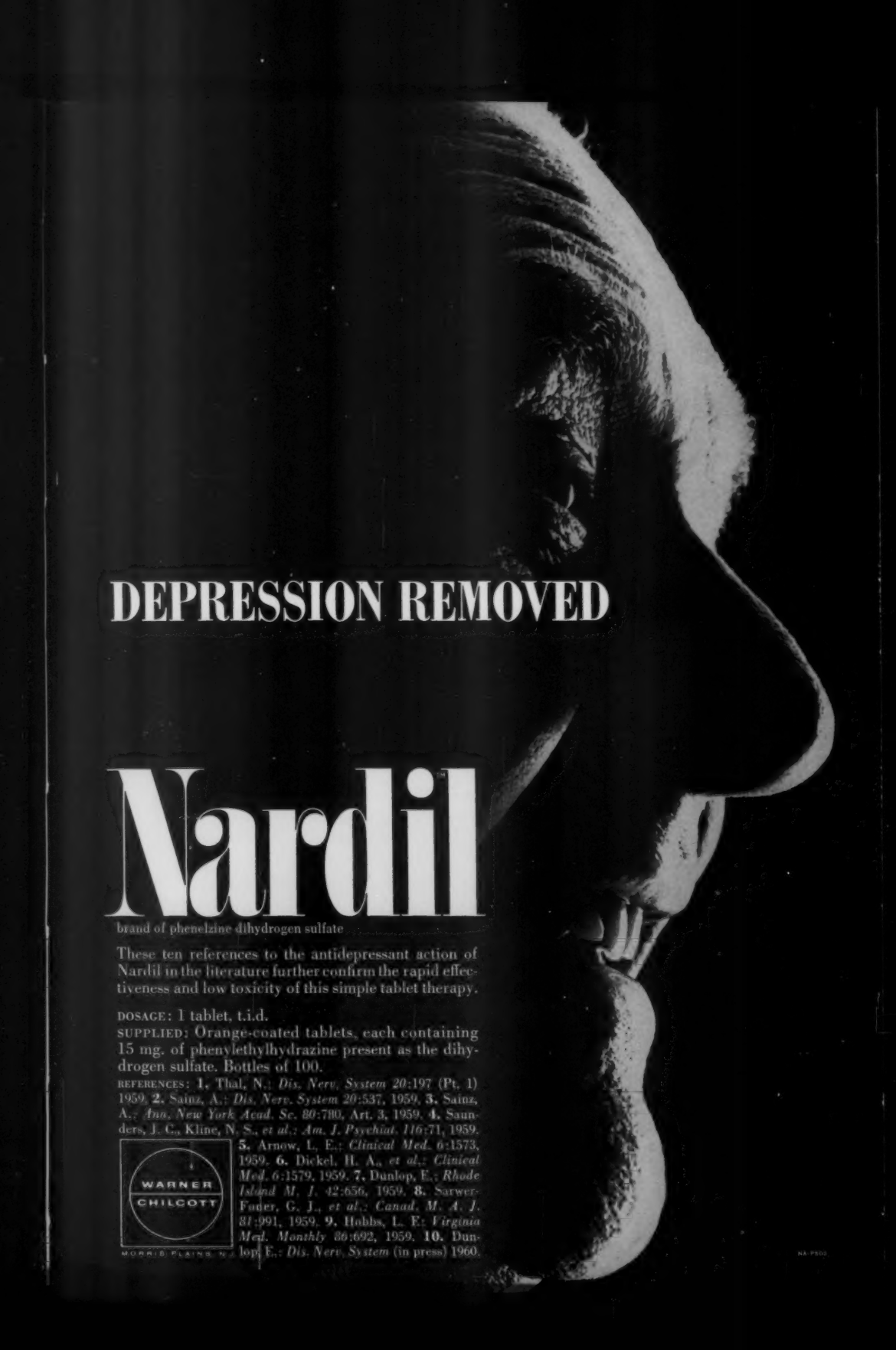
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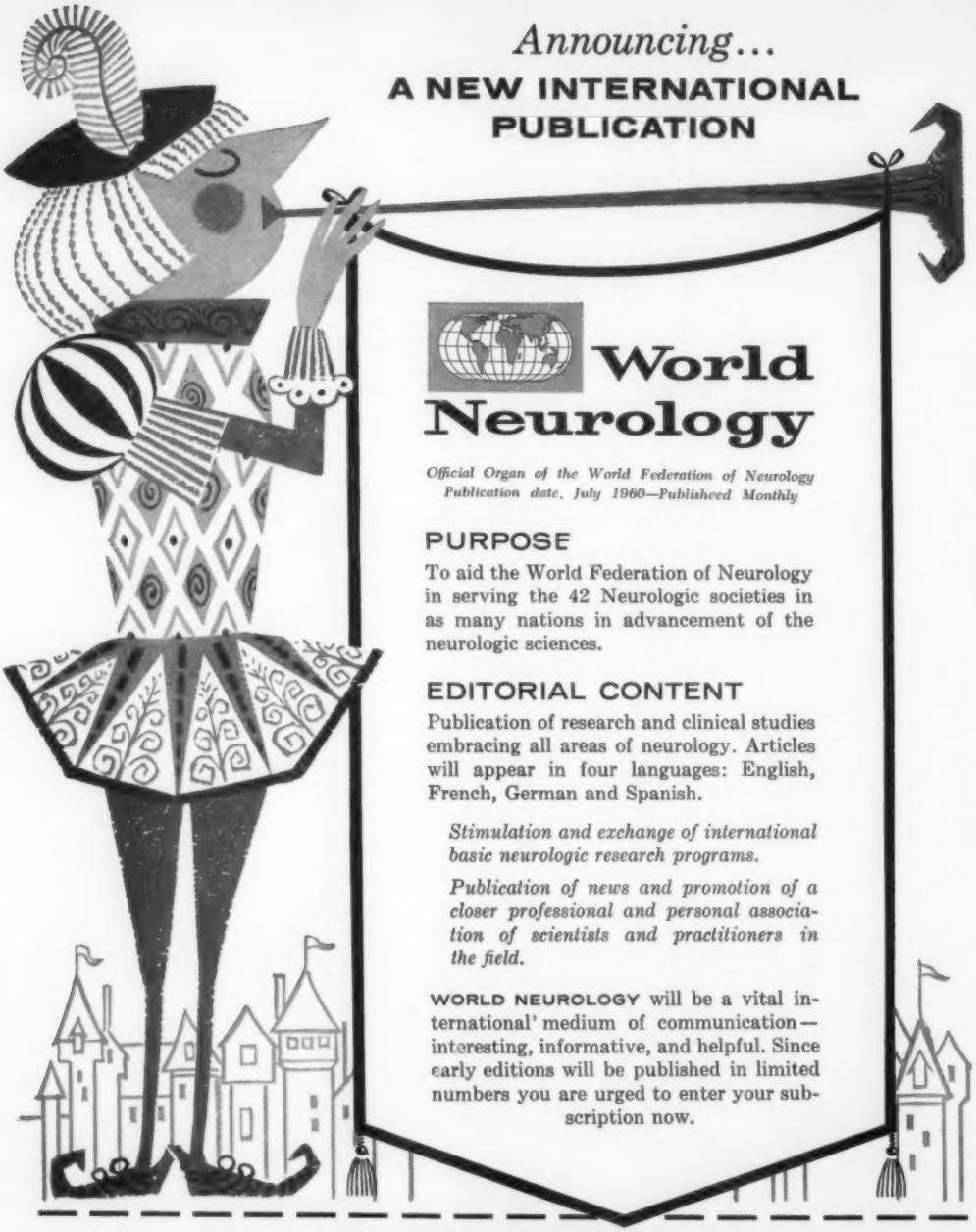

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1. Allen, V. S.: Trifluoperazine in the Treatment of Drug-Resistant Schizophrenics, J. Clin. & Exper. Psychopath. 20:247 (Sept.) 1959.

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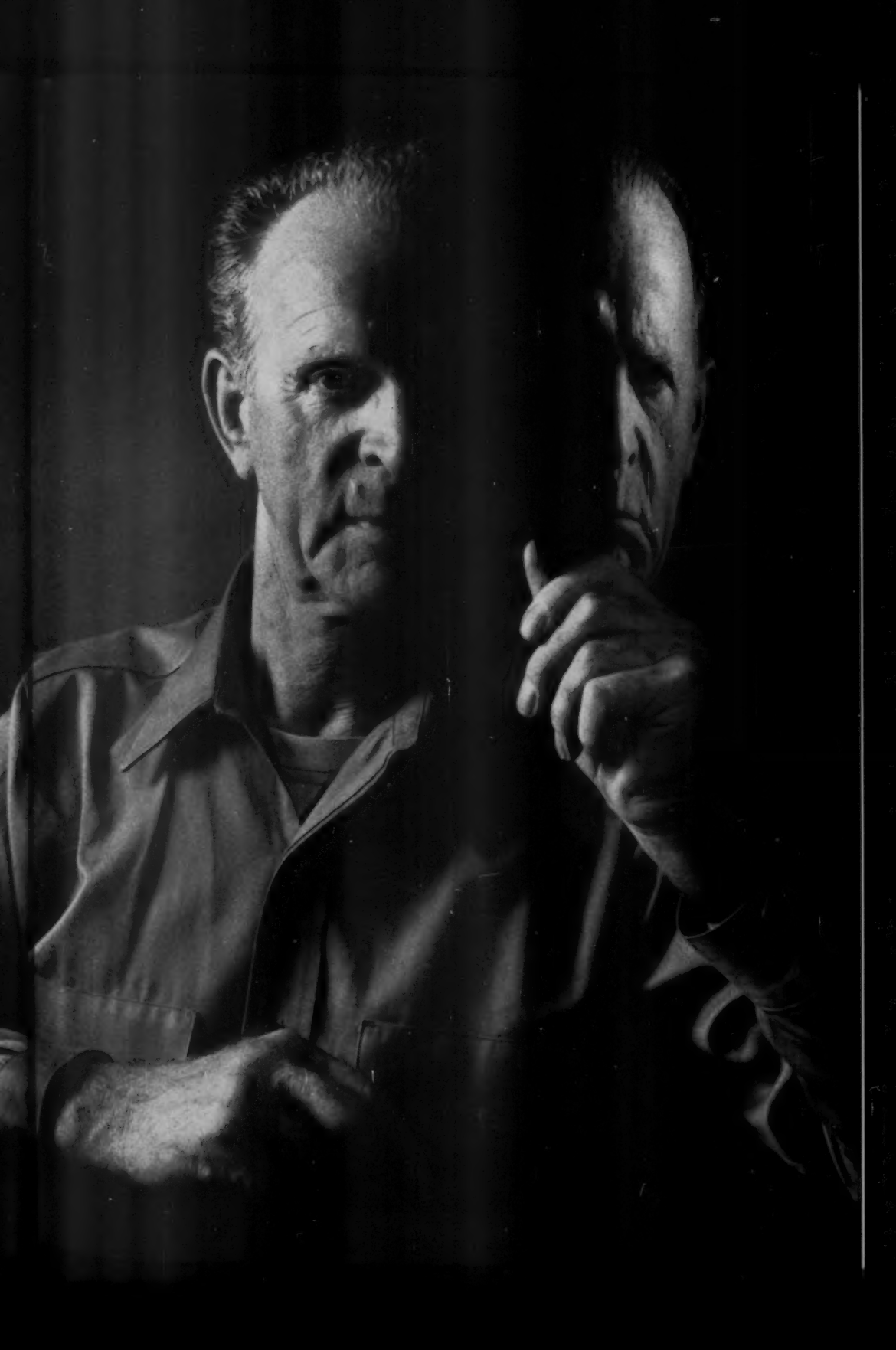

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Neurology Volume 10 • Number 5

Correlation of neurologic syndromes with lesions found angiographically

Report of 6 cases of cerebral arterial insufficiency

William S. Fields, M.D., Paul C. Sharkey, M.D.,
E. Stanley Crawford, M.D., and George C. Morris, M.D.

IN RECENT YEARS, considerable attention has been directed to the syndromes of intermittent insufficiency of the intracranial arterial systems. The patterns and significance of symptoms have been described by Millikan and Siekert,[1-3] who point out the difficulties often encountered in making the distinction between internal carotid and vertebral-basilar insufficiency. Unfortunately, this and other reports do not take into account 2 important factors: [1] the frequency with which anomalies occur within the circle of Willis, and [2] the multiplicity of atheromatous lesions in the major arteries supplying the brain.

In view of the increasing amount of evidence that many strokes are due to extracranial occlusive disease,[4-6] it has become necessary to employ precise methods of localization of lesions. Even though clinical evidence may suggest that the lesion is in the carotid system, it is often difficult to distinguish between intracranial and extracranial locations. The same difficulty exists in distinguishing between vertebral and basilar occlusive lesions. These considerations are particularly important when one is trying to determine whether an atheromatous lesion can be attacked surgically. It is the opinion of the authors that precise localization of these lesions is impossible without arteriographic examination.

All of the patients investigated in this study have been subjected to extensive arteriographic survey of the extracranial and intracranial arterial blood supply. These procedures have been performed under local anesthesia using 50% Hypaque and have caused no fatalities and no serious complications. By this method, considerable information has been obtained concerning anatomic anomalies, multiplicity of lesions, and collateral circulation. The data concerning collateral blood supply are being published elsewhere.

It is the purpose of this report to emphasize the difficulty of clinical localization of lesions without benefit of information obtainable only

From the Departments of Neurology and Surgery, Baylor University College of Medicine, Houston.
Read at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 16, 1959.

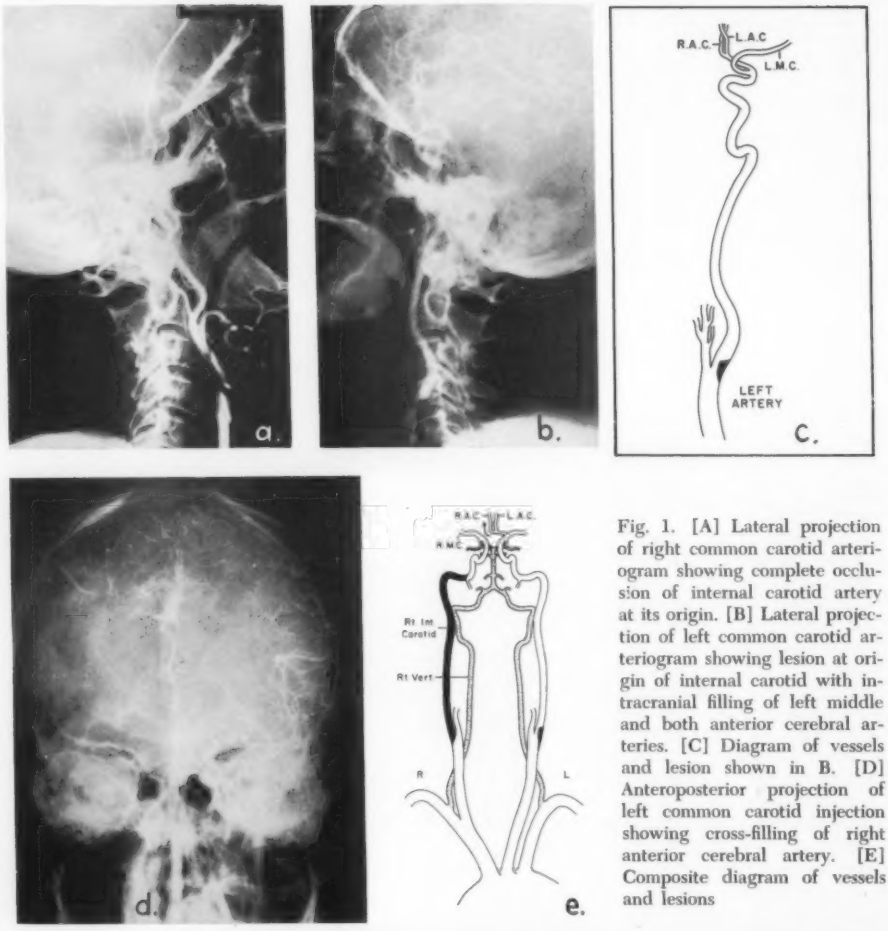


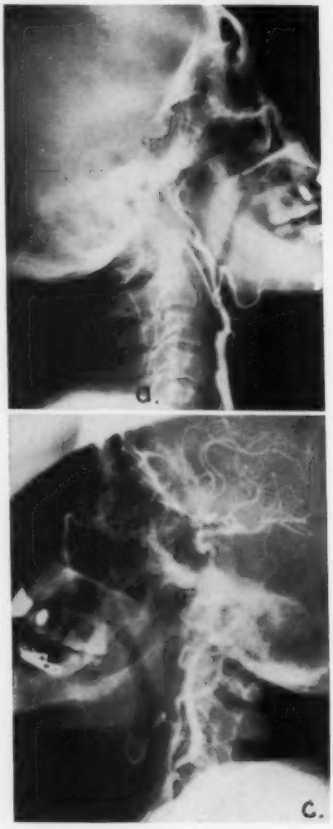
Fig. 1. [A] Lateral projection of right common carotid arteriogram showing complete occlusion of internal carotid artery at its origin. [B] Lateral projection of left common carotid arteriogram showing lesion at origin of internal carotid with intracranial filling of left middle and both anterior cerebral arteries. [C] Diagram of vessels and lesion shown in B. [D] Anteroposterior projection of left common carotid injection showing cross-filling of right anterior cerebral artery. [E] Composite diagram of vessels and lesions

with arteriograms. The following 6 cases illustrate some of the problems.

Case 1. A 65-year-old accountant was admitted in January 1958 with a history of recurrent motor symptoms involving the left upper extremity. In March 1954, he had experienced sudden onset of weakness in the left hand and difficulty in controlling the fingers. Involuntary movements were particularly notable in third and fourth digits. The weakness disappeared in a few hours, and the adventitious movements subsided after one week. In August 1954, he noted a "drawing sensation" in the left side of his face followed two days later by a moderately severe paresis of the left arm and face. The left leg was not involved. He recovered from the weakness in four days, but the involuntary movements returned and persisted.

Examination at the time of admission showed hyperactive reflexes in the left upper extremity, impaired stereognosis in the left hand, and athetoid movements of the fingers. The reflexes and motor power in the left leg were normal.

A right common carotid arteriogram revealed complete occlusion of the internal carotid artery with filling of the siphon through an external carotid-ophthalmic artery anastomosis. Left common carotid injection revealed stenosis of the internal carotid near its origin and intracranial filling of the left middle cerebral and both anterior cerebral arteries (Fig. 1).



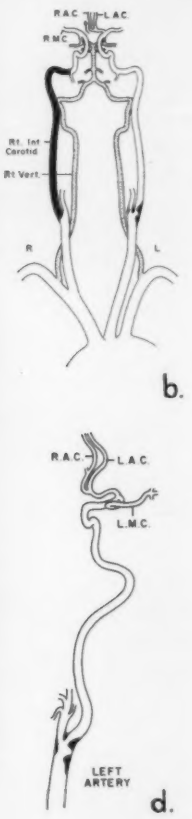


Fig. 2. [A] Lateral projection of right common carotid arteriogram showing complete occlusion of internal carotid artery at its origin. [B] Composite diagram of vessels and lesions. [C] Lateral projection of left common carotid arteriogram showing incomplete occlusion of internal and external carotid arteries in the region of the bifurcation and cross-filling of the right anterior cerebral artery. [D] Diagram of vessels and lesions seen in C

Comment. The focal nature of the neurologic signs and symptoms with noninvolvement of the left leg suggested a lesion in the branches of the right middle cerebral artery. Arteriographic study, however, demonstrated a lesion in the extracranial segment of the right internal carotid artery. Complete filling of both anterior cerebral arteries from the left is considered the probable explanation of the noninvolvement of the left lower extremity.

Case 2. A 67-year-old rancher was admitted in June 1958 because of sudden onset of left hemiplegia three weeks previously. Past history revealed an episode of sudden weakness in the left upper extremity in February 1957. The left leg was reported as not having been involved. Recovery from the weakness was complete after one month.

The episode that occasioned this hospital admission was one of left hemiplegia without sensory disturbance. There had been exaggerated reflexes on the left with Hoffman and Babinski signs. At the time of admission, persistent left upper monoplegia with hyperactive reflexes and left central facial paresis was noted. The Babinski sign was no longer present, and the patient was ambulatory with only slight residual weakness in the left lower limb.

A right common carotid arteriogram revealed complete occlusion of the internal carotid artery from its origin and no evidence of collateral filling of the intracranial branches. Left common carotid injection showed marked narrowing at the bifurcation in the neck and intracranial filling of the left middle and both anterior cerebral arteries (Fig. 2).

Comment. As in Case 1, there was marked involvement of the left upper extremity with only slight involvement of the lower extremity. In this instance, as in the previous one, both anterior cerebral arteries filled from the left internal carotid system. In Case 2, no collateral circulation was demonstrated, which may account for the more marked deficit. In neither case was there any evidence of cross-filling of the right middle cerebral artery.

Case 3. A 45-year-old housewife entered the hospital because of recurrent episodes of right hemiparesis, visual difficulty, and aphasia.

In October 1957, the patient had awakened early one morning with a sensation of choking and numbness of the right arm. She lost consciousness for about two minutes and then fully recovered without residual neurologic signs or symptoms.

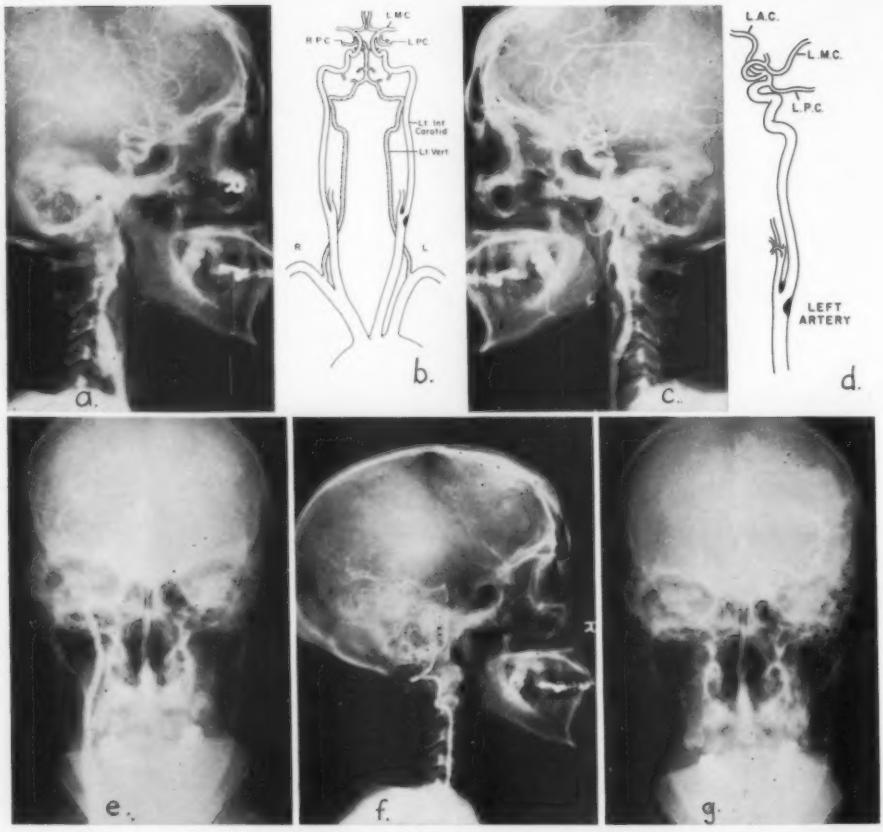


Fig. 3. [A] and [E] Lateral and anteroposterior projections of right common carotid arteriogram showing normal filling and distribution of vessels. [B] Composite diagram of vessels and occlusive lesion in left common carotid artery. [C] and [G] Lateral and anteroposterior projections of left common carotid arteriogram showing partial occlusion in distal portion of this vessel at origin of internal carotid. Left posterior cerebral artery fills from the carotid siphon. [D] Diagram of vessels and lesion shown in C and G. [F] Lateral projection of right vertebral arteriogram showing no evidence of occlusion. Only the right posterior cerebral artery fills from the basilar artery. (This was also evident in anteroposterior projection, but photographic reproduction was inadequate.)

An electroencephalogram made after this attack showed left temporal slow wave focus. Another recording in December 1957 was considered normal.

Early in January 1958, she had a similar episode but this time on regaining consciousness was found to have motor aphasia, right hemiplegia, and right homonymous hemianopia. The aphasia and visual field defect cleared in two days and the hemiplegia in five days. The same symptoms and signs recurred on the night of the fifth day with gradual return to normal over the next two weeks. An electroencephalogram recorded at this time revealed once again left temporal slow wave focus.

On November 11, 1958, the patient had a transient attack of dysphasia, right hemiparesis, and loss of vision to the right which lasted about ten

minutes. Three days later, she was admitted to the hospital. At that time, no abnormality was noted in the neurologic examination. An electroencephalogram still showed a left temporal focus of slow activity in the resting record. Left carotid compression did not alter the tracing. Right carotid compression produced bilateral slowing most pronounced on the left. This was interpreted as being indicative of insufficiency of the left internal carotid system.

A right common carotid arteriogram showed good filling of the right anterior and middle cerebral branches and of the right internal carotid artery from its origin. Left common carotid injection showed an atheromatous plaque partially occluding the distal portion of this vessel and the origin of the internal carotid artery. Good filling of the left anterior, middle, and posterior cerebral arteries from the internal carotid was also seen. A right vertebral arteriogram showed no evidence of atherosclerosis in that vessel or the basilar artery. Only the right posterior cerebral artery filled from the vertebral-basilar system (Fig. 3).

Using a temporary bypass shunt, left carotid endarterectomy was performed successfully. Two weeks after surgery, an electroencephalogram showed no evidence of focal abnormality and the tracing was not altered by carotid compression. The patient has had no recurrence of symptoms during the ensuing seven months.

Comment. The origin of the left posterior cerebral artery as well as the anterior and middle cerebral vessels from the left internal carotid artery probably accounts for the homonymous field defect present during the patient's attacks. Visual disturbance of this character is more frequently associated with vertebral-basilar insufficiency and in such instances may be bilateral.[7]

Case 4. A 47-year-old farmer was admitted to the hospital in June 1958 because of sudden onset of visual disturbance and quadriparesis five days previously. By the time of his admission, he had recovered from all of his symptoms except for difficulty in seeing to the left. Examination was normal except for left homonymous hemianopia.

Bilateral vertebral and common carotid arteriograms were performed. The carotid injections did not reveal any abnormality, but it was noted that the left posterior cerebral artery filled from the carotid system. The right vertebral artery failed to fill from the subclavian injection and was considered to be completely occluded. The left vertebral artery showed a marked narrowing at its origin from the subclavian. Only one posterior cerebral artery filled from the basilar system and was thought to be the right since the left filled from the carotid system.

Left vertebral endarterectomy was performed, and, except for persistent left upper homonymous quadrantanopia, the patient had no neurologic signs nor any recurrence of symptoms thirteen months later.

Comment. This case was clearly one of vertebral-basilar system insufficiency, but, on the clinical grounds alone, localization of the arterial obstruction was impossible.

The visual field defect was unilateral homonymous hemianopia rather than bilateral in this instance because, as in Case 3, one posterior cerebral artery filled from the basilar system and the other from the carotid. In many cases of basilar arterial insufficiency, hemiparesis rather than quadriparesis may occur, as in Case 5. It is evident from these observations that hemiparesis with hemianopia cannot be considered diagnostic of involvement of one system rather than another unless additional signs or symptoms are present.

Case 5. A 68-year-old retired grocer was admitted to the hospital on March 2, 1959, because of severe intermittent claudication in both legs.

History was obtained at that time of an episode in September 1958 of sudden onset of numbness of the right face while he read his morning newspaper. This was followed by momentary loss of vision and inability to use the right arm and leg. Speech was not affected. Recovery was complete in fifteen minutes.

At the time of admission, neurologic examination was considered to be normal. A loud systolic murmur over the left common carotid bifurcation and a soft systolic murmur in the right supraclavicular region were heard.

On March 4, 1959, a thoracic angioaortogram was performed with 50 cc. of 85% Hypaque injected into the right antecubital vein. This revealed narrowing of the left common carotid and subclavian arteries at their origin from the aortic arch and also suggested the presence of lesions in the bifurcations of both common carotid arteries (Fig. 4A).

The next morning, the patient had transient left hemiparesis that cleared in about one hour without residual. This was considered to be evidence of either bilateral carotid involvement, as suggested radiographically, or basilar insufficiency. The latter seemed to be a distinct possibility in view of the history of complete transient visual loss with the first attack.

A right subclavian-vertebral arteriogram revealed several points of narrowing in the distal intracranial segment of the vertebral artery. Bilateral common carotid injections also disclosed lesions in both carotid bifurcations but most marked on the left, the side with the audible murmur. A left subclavian-vertebral arteriogram showed a patent but hypoplastic vertebral artery (Fig. 4).

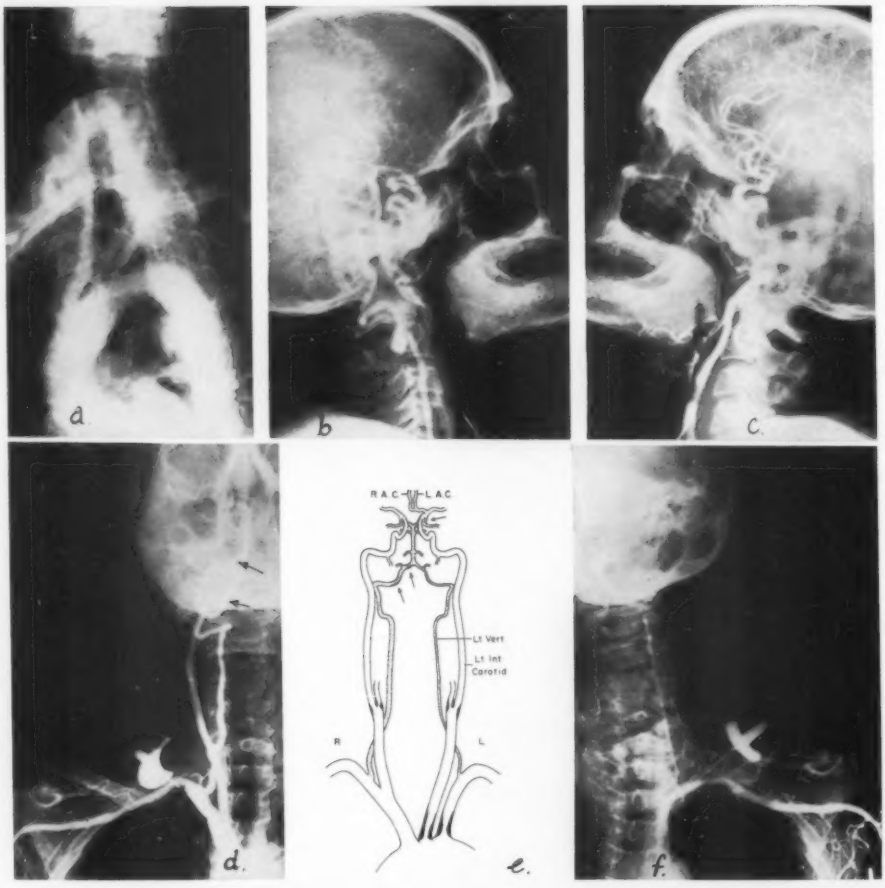


Fig. 4. [A] Thoracic angioaortogram showing narrowing of the left common carotid and left subclavian arteries near their origin from the aortic arch. [B] and [D] Lateral and anteroposterior projections of right subclavian arteriogram showing normal extracranial filling of vertebral artery and partial occlusion in origin of right internal carotid artery; 2 separate points of significant narrowing (arrows) are shown in the distal portion of the right vertebral artery. [C] Lateral projection of left common carotid arteriogram showing partial occlusion in the bifurcation of this vessel. Both anterior cerebral arteries fill from the left carotid system. [E] Composite diagram of vessels and multiple lesions. [F] Anteroposterior projection of left subclavian arteriogram showing normally filled but hypoplastic vertebral artery

In view of the marked intracranial involvement of the vertebral-basilar system and the small left vertebral artery, the patient was not considered to be a candidate for vascular surgery.

Comment. At the time of admission, the history and physical findings suggested internal carotid insufficiency on the left side, and this appeared at first to be confirmed by angiograms. However, the subsequent occurrence of left hemiparesis focused attention on the possibility of bilateral carotid or basilar insufficiency. The latter seemed more likely in view

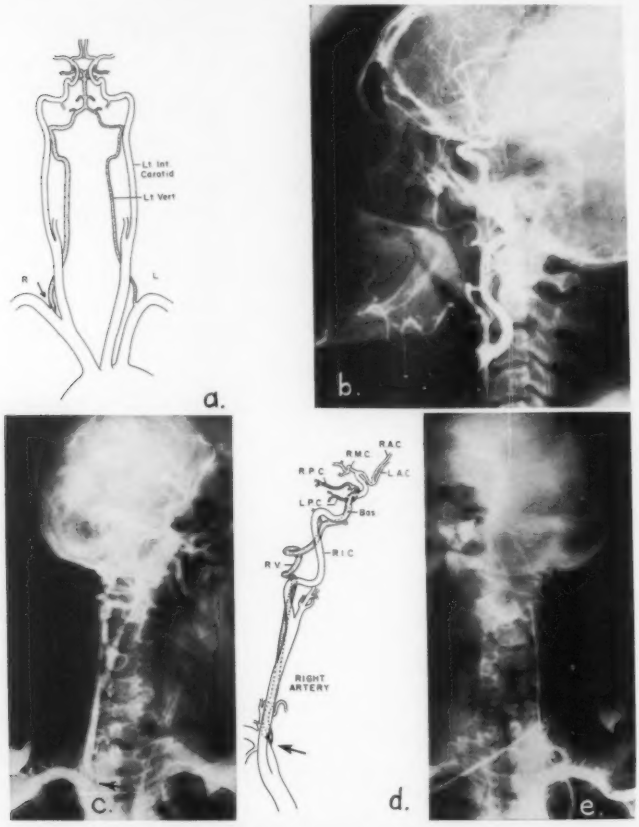


Fig. 5. [A] Composite diagram of vessels and lesion. [B] Lateral projection of left common carotid arteriogram showing normal filling of vessels without evidence of occlusion. [C] Anteroposterior projection of right subclavian arteriogram showing good filling of both vertebral-basilar and carotid systems. Narrowing of the right vertebral artery at its origin is evident. There is no evidence of other occlusive lesions. [D] Diagram of vessels and lesion shown in C. [E] Anteroposterior projection of left subclavian arteriogram showing hypoplastic but well-filled vertebral artery

of the history of apparent bilateral homonymous hemianopia with the patient's previous attack. This could not have been established with any degree of certainty without use of vertebral arteriograms.

Case 6. A 63-year-old business executive was admitted to the hospital in January 1959 because of recurrent episodes of visual disturbance, dizziness, and unsteadiness of gait. His first attack had occurred in November 1958 with sudden onset of dimness of his entire vision followed by a sensation of loss of balance, so that he had to hold on to something to keep from falling. During the next month, he had 5 or 6 similar attacks. On some occasions when his vision improved, diplopia was present. On other occasions, there were associated numbness and tingling in the perioral region. Duration of these episodes was from five to fifteen minutes.

On December 24, 1958, while driving his car,

he suffered a sudden complete loss of vision. This improved but never returned to normal.

At the time of his admission, examination revealed right homonymous central scotomas but was otherwise negative except for evidence of mild diabetes mellitus.

Bilateral carotid and veterbral arteriograms revealed only involvement in the vertebral-basilar system. The right vertebral artery was shown to have marked narrowing at its origin from the subclavian artery, while the left vertebral was noted to be a much smaller vessel. No lesions were noted in the distal portion of the vertebral-basilar system (Fig. 5).

Right vertebral endarterectomy was performed at the origin of the artery in the supraclavicular region and a Dacron patch inserted. The patient's vision has gradually improved, but relative scotomas still persist. During the five months since surgery, the patient has had no further episodes of transient arterial insufficiency.

Comment. Although the clinical evidence supported a diagnosis of basilar insufficiency, precise localization of a lesion was impossible without arteriograms. The lesion might have been intracranial, as in Case 5, rather than extracranial. In the former location, surgery would have been impossible.

DISCUSSION

The 6 cases included in this report were selected from among more than 300 patients with suspected occlusive cerebrovascular disease in whom angiographic studies were carried out. All of these procedures were performed under local anesthesia using Hypaque as a contrast medium.[8,9] No fatalities occurred in this series; 1 patient had hemiparesis that lasted twenty-four hours, and 3 others had focal seizures during the procedure with no residual deficit. On numerous occasions, injections were made in one common carotid artery with the full knowledge that the contralateral internal carotid was completely occluded. This has not resulted in any complications.

These observations are in marked contrast to those of Sugar and Bucy[10] with respect to vertebral arteriographic study and contrary to the admonition of Johnson and Walker[5] in their review of spontaneous carotid thrombosis. As recently as May 1958, Siekert and Millikan,[3] citing these authorities, wrote, "Cerebral angiography, especially through the vertebral arteries, probably is best avoided, since the risks from this procedure are increased if cerebrovascular disease is present," and "arteriography carries certain hazards in the presence of cerebrovascular disease, and we believe that it should be restricted in use."

It is the opinion of the authors that cerebral arteriographic study carries no increased risk in the presence of atherosclerosis if one uses reasonable caution and performs the procedure under local anesthesia to avoid hypotension. In addition, the frequency with which complications are encountered in arteriographic examination in general has been greatly reduced in the past three years with the introduction of newer contrast media and technics more refined than those in use when the abovementioned reports were published.

The authors also submit the opinion that the precise localization of lesions in the cases cited in this report would have been impossible without the employment of arteriograms. This is especially significant when one is endeavoring to find lesions that may be removed or corrected by vascular surgical technics.

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Interaction of viruses with native brain substrates

Samuel Bogoch, M.D., Ph.D.

While viruses are relatively simple biologic agents, little is known of the manner in which they invade the host cell, propagate therein, and leave for new host cells. The process is an extremely single-minded one, so to speak; the virus must enter a living cell in which its nucleic acid can be reproduced for as long as the cell serves the necessary metabolites.

Most efforts toward interruption of the viral-host sequence have been unsuccessful. Agents that are toxic to virus protein and virus nucleic acid are also potentially toxic to host cell protein and host cell nucleic acid. Furthermore, the concept of the antimetabolite does not appear to apply, since, although bacteria need to take in metabolic substrates from the surrounding environment and to utilize these in a metabolic pool, the virus does not. The virus cannot exist on extracellular metabolites but must enter the cell and, even there, does not take in metabolites in the usual bacterial sense but appears to organize the whole of the cell's biologic economy to reproduce itself.

Since the virus does not take in extracellular metabolites, it cannot take in any extracellular antimetabolites. Another therapeutic approach is therefore indicated. One that has been developed in recent studies[9,10] at this laboratory will be outlined briefly. Essentially, it consists of the use of isolated substances that resemble the native chemical receptors for the virus in order to decoy the virus away from the cell and thus to prevent its entry.

Beginning with the work of Hirst[1,2] defining the presence of specific chemical receptors on the red cell surface to which many viruses attach themselves, the concept of specific viral receptors has gained impetus through the work of Gottschalk[3] and Klenk.[4,5] From these studies, the suggestion arose that neuraminic acid might be the receptor substance in the red blood cell to which the virus attaches itself. Studies on the structure of a large molecular weight glycolipid called brain ganglioside,[6–8] which occurs almost exclusively in the gray matter of brain and contains approximately 30% of its weight as neuraminic acid, led to the consideration of the possibility that this material might be a native receptor substance in gray matter for infecting viruses. By Hirst's method for viral hemagglutination,[1,2] viruses, when added to a suspension of red blood cells, caused the agglutination of these cells in a manner that is readily determinable. Several nonspecific, poorly characterized inhibitors of this reaction are known.[3] Many of these are impure mucoprotein fractions that occur in blood serum, meconium, ovarian cyst fluid, and urine. The chemical structure of none of these inhibitors is known. During the course of studies on the chemical structure of brain ganglioside, it seemed important to determine whether this substance might act as an inhibitor of the viral hemagglutination reaction. If it did, one at once would have a large molecular weight material native to gray matter of brain which bound virus in vitro and had a reasonably well known structure. It was found that brain ganglioside did indeed inhibit the hemagglutination reaction of influenza PR8 and NWS viruses in extremely low concentrations, as low as 0.3 μg. per tube.[9] This inhibition was shown to be relatively

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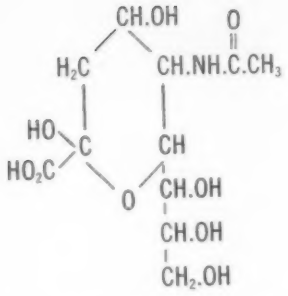

Fig. 1. Structure of neuraminic acid

specific to the structure of brain ganglioside; all but one of its hydrolytic fractions were quite negative in the effect, but the fraction that contained neuraminic acid and a small amount of galactosamine was active by itself, although not as active as the intact molecule.

Figure 1 shows the structure of neuraminic acid as recently determined in the synthesis of Cornforth, Firth, and Gottschalk.[11] One can see that it is a hexosaminouronic acid, that is, it contains characteristics of both an amino acid and an amino sugar.

Figure 2 shows the structure of brain ganglioside as it has been determined in hydrolytic studies in our laboratory.[6–8] It may be seen that neuraminic acid comprises approximately 30% of this repeating unit. The molecular weight of this unit is approximately 3,314, and 70 to 80 of these units are polymerized to form the entire macromolecule brain ganglioside, molecular weight approximately 250,000.

Figure 3 shows the structure and analytical data of one of the basic constituent units of brain ganglioside, isolated by hydrolysis of intact brain ganglioside, a substance previously unknown, called gangliocerebroside.[7,8] It is composed of 1 mole of glucose, 1 mole of sphingosine, and 1 mole of stearic acid. The elemental analysis and some of the physical constants determined for this material are shown.

By means of the isolation of other hydrolytic fragments such as gangliodicerebroside,[8] consisting of 2 moles of gangliocerebroside and 1 mole of hexose, the structure shown in Figure 2 was arrived at. It may be seen that this proposed structure shows brain ganglioside to have a water-soluble surface and a lipid-soluble surface, an arrangement ideally suited for function at a membrane site that separates aqueous and lipid soluble phases. These structural considerations led to the suggestion that brain ganglioside might be involved in membrane, receptor, and transmission functions in the nervous system.[8]

Table 1 shows the use of ash-free brain

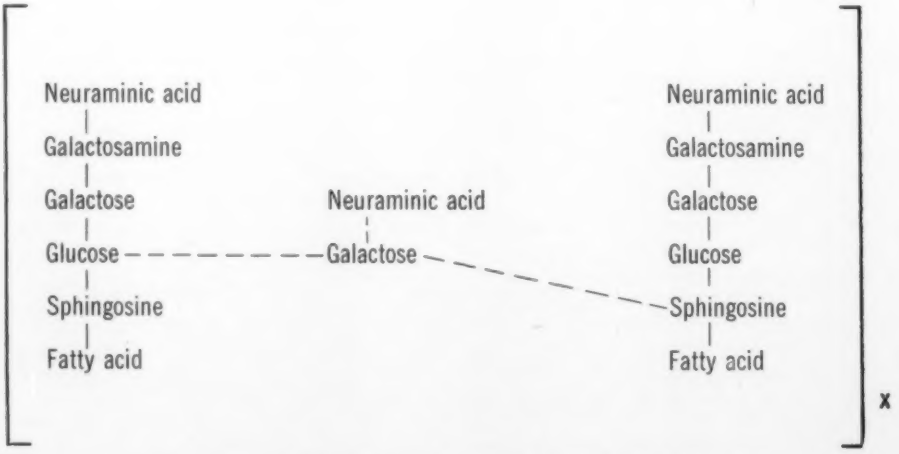

Fig. 2. Proposed structure of basic repeating unit of brain ganglioside

GANGLIOCEREBROSIDE

Glucose

Sphingosine

Stearic acid

$C_{42}H_{81}O_8N$ (H_2O)

Melting point, 172 to 174° C.

Iodine number 23.2

$[\alpha]_D^{20}$ – 2.08

X-ray diffraction spacings at 2.41, 4.10, 9.1, 10.4, 15.6, 21.1, 30.6, 49.2, 55.5, and 63.5 Å

	% C	% H	% N	% Hexose (as glucose)
Found	67.13	10.95	1.86	21.8
Calculated	67.65	11.14	1.88	22.0

Fig. 3. Structure and analytic data on gangliocerebroside

ganglioside and its hydrolytic derivatives to test their ability to bind virus in vitro in the hemagglutination inhibition reaction. It can be seen that intact brain ganglioside inhibits the hemagglutination reaction. Whereas the bulk of the molecule containing all of the lipid and all of the hexoses is totally ineffective, the fraction containing neuraminic acid and hexosamine is active, although not as active as the whole molecule, in binding virus. This situation is reminiscent of that which we have come to know in the prosthetic group–protein relationship of enzymes; that is, there is a prosthetic group (in this case, neuraminic acid–galactosamine) most intimately involved with the specific chemical reaction, but its effectiveness is much increased by the fact that the macromolecular substance (in this case, a glycolipid) apparently orients the prosthetic group optimally in space.

This, then, appears to be the first marcromolecular glycolipid substance that binds virus and has a reasonably well defined structure. At the same time, the quite independent work of Kozloff[12] on the effect of hexosamines rather than neuraminic acid on viral invasion had demonstrated that a virus particle released its nucleic acid in the test tube under the stimulus of hexosamines and amino acids. It occurred to me that a 2-stage mechanism for the invasion of viruses into the nerve cell might be operant, consisting of hydrolytic removal of neuraminic acid followed by galactosamine-induced transfer of viral nucleic acid into the cell;[9] that is, the virus approaches the cell receptor, which presents neuraminic acid outermost. It is of interest to note that the acidity of neuraminic acid is such that it would effectively denature the nucleic acid of the virus. It is also of interest to note that the only intact enzyme function demonstrated for the extracellular virus is its neuraminidase function; that is, the virus possesses the ability to cleave neuraminic acid from its glycosidic binding to macromolecules. One might say that it would be not only useful but essential that neuraminic acid be removed from the path of the virus in order that it might enter the cell, and, in fact, this appears to be what the virus does. A further point of interest now arises with regard to the structural sequence that we determined for brain ganglio-

TABLE 1
HEMAGGLUTINATION INHIBITION ACTIVITY OF BRAIN GANGLIOSIDE AND ITS HYDROLYTIC SUBFRACTIONS*

Procedure	Fraction	Dry weight as % of ash-free ganglioside	Analysis of fraction: % of fraction — Neuraminic acid	Nitrogen	Hexose	Reducing sugar	Galactosamine	Hemagglutination inhibition activity
1. Autohydrolysis of ash-free brain ganglioside at 100° for 20 minutes followed by dialysis	Ash-free brain ganglioside	100.0	30.3	2.9	24.0	0	10.0	Positive from 20 mg. to 0.3 μg.
	1 Neuraminic acid fraction I (Dialyzable)	20.8	88.0	4.42	0.75	45.0	2.5	Positive from 500 μg. to 125 μg.
2. Partition of neuraminic acid fraction I with cold methanol	2 Crystalline neuraminic acid (insoluble in cold methanol)	9.0	100.0	4.5	0	61.4	0	Negative
	Residue A (non-dialyzable)	81.0	13.0	2.7		0		Negative
3. Hydrolysis of residue A with 0.09N HCl at 100°	3 Crystalline glucostearocerebroside (water-insoluble)	30.0	0	1.86	21.8		0	Not tested because water-insoluble

side, that is, the accompaniment of neuraminic acid by a galactosamine molecule. Once the virus has cleaved neuraminic acid, it would be in an immediate relationship to the hexosamine, which is a substance that induces the release of the viral nucleic acid from its protein overcoat. At the cell membrane, this might be the triggering mechanism for the transfer of viral nucleic acid into the cell.

With this 2-stage mechanism for the entry of viruses into the cell in mind, it became of interest to determine, if this 2-stage mechanism in fact operated, whether it would be possible to intercept the virus by presenting to it an extracellular receptor substance so close in structure to the membrane receptor substance of the cell that the virus would attach itself to the decoy and thus not enter the cell. The following animal experiments were then undertaken with the assistance of Dr. Alvin S. Levine.[10] The bioassay system used was that well described by the Henles,[13] consisting of the injection of active virus intracerebrally into mice and observation of the resultant convulsions and death that ensued in the next few days. If the mouse is twirled by the tail for a fixed number of times at twenty-four- or forty-eight-hour intervals after the virus has been injected, severe grand mal convulsions result. Brain ganglioside injected intracerebrally at the same time was shown to inhibit the neurotoxic effect of influenza PR8 and NWS viruses.[10]

Figure 4 shows the percentage of mice that convulsed when 154 HA* units of PR8 virus were given and when 31 HA units were given alone. With the higher concentration of virus

*Hemagglutin titer

0.15 γ per mouse of brain ganglioside did not have any effect; 3 γ reduced to 83% and 15 γ reduced to 67% the number of mice that convulsed. A viral dose reduced to 31 HA units was still sufficient to produce convulsions in 100% of the mice; here we can see the quantitative aspect of the inhibitory viral combination. Thus, 0.15 γ of ganglioside here reduced to 83%, 3 γ reduced to 20%, and 15 γ reduced to 10% the number of mice that convulsed. Comparing this group with the previous group, an almost unit for unit titration phenomenon of virus by inhibitor is suggested. The inhibitor was also effective if given two hours after the virus or two hours before the virus (PR8).[10] When given two hours before PR8 virus, the per cent of mice convulsed was reduced from 90 to 30, but, two hours after the virus, the per cent of mice convulsed was reduced little, if at all. On the other hand, Table 2 shows that, in the case of the more neurotropic strain of influenza virus, NWS, the inhibitor had a definite effect even two hours after the virus was given, reducing the per cent of mice convulsing from 73 to 8. There seems to be a difference between the non neurotropic strain PR8 and the neurotropic strain NWS in terms of their susceptibility to the action of the inhibitor when used therapeutically after the injection of virus.

Table 3 shows the inhibitor-virus combination that has also been demonstrated in tissue culture.[10] Using the chorioallantoic membrane of the chick, the hemagglutination development was inhibited by the same concentration range of inhibitor as that which was active in the red blood cell inhibition and in the in vivo tests in mouse brain. The inhibitor has not yet been tested in any species other than mouse.

In conclusion, chemical studies on the structure of brain ganglioside have suggested that it is a viral receptor in gray matter of brain. Purified brain ganglioside has been shown [1] to combine with virus in the test tube and to effectively compete with the red blood cell for the virus; [2] to combine with virus in

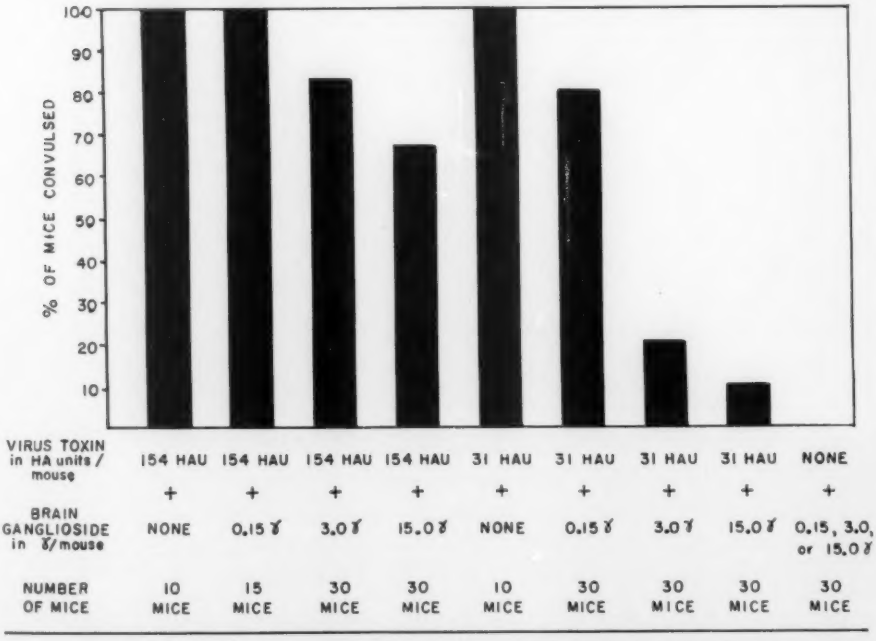
% OF MICE CONVULSED
100
90
80
70
60
50
40
30
20
10
VIRUS TOXIN in HA units / mouse
154 HAU + | 154 HAU + | 154 HAU + | 154 HAU + | 31 HAU + | 31 HAU + | 31 HAU + | 31 HAU + | NONE +
BRAIN GANGLIOSIDE in γ/mouse
NONE | 0.15 γ | 3.0 γ | 15.0 γ | NONE | 0.15 γ | 3.0 γ | 15.0 γ | 0.15, 3.0, or 15.0 γ
NUMBER OF MICE
10 MICE | 15 MICE | 30 MICE | 30 MICE | 10 MICE | 30 MICE | 30 MICE | 30 MICE | 30 MICE

Fig. 4. Inhibition of neurotoxic effect of influenza PR8 virus by brain ganglioside

TABLE 2

INFLUENCE OF BRAIN GANGLIOSIDE UPON THE NEUROTOXIC EFFECT OF INFLUENZA PR8 AND NWS VIRUSES[10]

Group	Number of mice	Virus toxin injected (HA units per mouse)	Brain ganglioside injected (μg. per mouse)		Per cent of mice convulsed	
			With toxin	2 hours after toxin	At 30 hours	At 48 hours
a. PR8: I	10	154	0	0	90	100
II	10	31	0	0	90	100
III	30	154	15.0	0	87	67
IV	30	31	15.0	0	38	10
V	30	154	3.0	0	77	83
VI	30	31	3.0	0	53	20
VII	15	154	0.15	0	93	100
VIII	30	31	0.15	0	93	80
IX	10	0	15.0	0	0	0
X	10	0	3.0	0	0	0
XI	10	0	0.15	0	0	0
						At 43 hours
b. NWS: 1	10	640	0	0		80
2	11	160	0	0		73
3	5	16	0	0		20
4	5	1.6	0	0		20
5	14	640	15.0	0		86
6	10	160	15.0	0		33
7	13	640	0	15.0		69
8	12	160	0	15.0		8

TABLE 3

TISSUE CULTURE CONTACT TEST

*Reciprocal of viral HA titer from triplicate experiments with varied concentration of brain ganglioside**

Concentration of ganglioside	None		50 μg. per cc.		25 μg. per cc.		5 μg. per cc.	
Time of incubation	48 hours	72 hours	48 hours	72 hours	48 hours	72 hours	48 hours	72 hours
$TCID_{50}$								
100	16	64	< 2	32	16	64	32	128
	16	64	< 2	32	4	64	8	—
	16	64	4	32	4	64	16	128
10	< 2	32	< 2	8	< 2	32	< 2	64
	< 2	32	< 2	16	< 2	32	< 2	64
	< 2	32	< 2	16	< 2	64	< 2	128
1	< 2	16			< 2	< 2	< 2	< 2
	< 2	64			< 2	4	< 2	< 2
	< 2	64			< 2	< 2	< 2	< 2

*$TCID_{50}$ is the infective dose of PR8 virus inoculated per tube. Concentration of ganglioside is the final concentration per milliliter of tissue culture.

tissue culture and to prevent the development of viral hemagglutinins; and [3] to inhibit the neurotoxic effects of influenza PR8 and NWS viruses in mouse brain.

These findings suggest a new approach to the control of viral infections in man, that is, the presentation to the virus of substances sufficiently chemically akin to the natural receptors that the virus attaches itself to the decoy material and leaves the normal cell unharmed. Further implications of these findings are suggested by other studies by Dr. Elenore Bogoch and I[14] which demonstrated that brain ganglioside is also a membrane-active material that can stimulate the clam heart in the low concentration range at which serotonin and acetylcholine are effective. These studies combined with the virus studies presented here offer clues relative to the possible membrane function of brain ganglioside in the nerve cell in relation to the transfer not only of viruses across the membrane but also of inorganic salts and other body metabolites. Here, questions of the chemical basis of nerve impulse transmission and the blood-brain barrier come sharply into focus. It is further possible that a large family of substances throughout the body, which are chemically related to brain ganglioside with reference to their content of neuraminic acid and hexosamine, will be found to serve similar purposes in the membrane function of the cells in which they are located. If such is the case, a glimpse shall have been caught of the chemical basis for some of the functions of the living cell membrane.

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Preliminary observations on abnormal catecholamine metabolism in basal ganglia diseases

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DURING the last few years, much work has been done toward the understanding of extrapyramidal disorders after use of tranquilizers and ganglioplegics in man and animals.[1–5] The mechanism of action of reserpine and other "narcoleptics" has been linked with the metabolism of norepinephrine and serotonin. Reserpine is known to produce a marked depletion of body stores of these substances,[6,7] while iproniazid induces their accumulation in the brain.[8] Precise maps of the various catecholamines in the brain and their enzyme systems have been drawn up and their concentration measured.[9–11] Carlsson[12] recently demonstrated the presence of 3-hydroxytyramine (dopamine) within the brain, particularly within the basal ganglia.[13] Tremors in Parkinson's disease and nicotine-induced tremors in animals have been shown to be increased by injections of epinephrine,[14–16] while other strange hyperkinesias have resulted from injections of IDPN (beta-beta'-iminodipropionitrile) and tryptamine derivatives (DMT and T-9).[17,18] Finally, some interesting correlations have been suggested concerning the role of ceruloplasmin in epinephrine and serotonin metabolism as well as in Wilson's disease.[19–21]

These facts suggested to us that a disorder in catecholamine metabolism may be present in some basal ganglia diseases. Our communication can be only preliminary because of the unspecific nature of some of the experiments performed, but the pattern of results indicates that further chemical identification and verification is justified.

MATERIAL AND METHODS

We chose to do the determinations on urines and to use 2 methods. At first, we employed a simple colorimetric determination based on the oxidation of epinephrine-like products in the presence of iodine to give a red color.[22] This is known as Simola's reaction;[23] 2 cc. of fresh urine are heated with 5 drops of Lugol solution and the urine then extracted with butyl alcohol. A bright red or deep pink color to the supernatant indicates a positive reaction. This method was used on 32 patients. We then supplemented this procedure by a bioassay on a strip of rabbit aorta as described originally by Helmer[24] for the detection of pheochromocytoma and as modified by Arnold and Rotschild.[25] The assay is based on the contraction of a spirally cut strip of rabbit thoracic aorta in a muscle chamber. The strip is bathed in Krebs bicarbonate solution, and through this solution a constant flow of a 95:5 mixture of oxygen and carbon dioxide is bubbled. The contraction is recorded through a lever on a drum of "waxed paper" and compared to the contraction obtained on the same strip with a standard of norepinephrine. The apparatus used in this study was built by Rotschild and Arnold and will be described by them elsewhere. For purposes of this study, a "positive" reaction is one equal at least to the contraction obtained with a urine containing an equivalent of 200 μg. of epinephrine per day. The urines of 44 patients were tested by such a bioassay; 27 of these had been checked by Simola's reaction. Complete agreement between the 2

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TABLE 1
SIMOLA'S REACTION

	Number	Per cent
Total Urines Verified	234	100.0
Positive	68	29.0
Negative	166	71.0
Total Urines, basal ganglia cases	109	100.0
Positive	65	59.6
Negative	43	40.4
Total Urines, nonbasal ganglia cases	126	100.0
Positive	3	2.3
Negative	123	97.7

methods, both for positive and negative results, was obtained. In all cases, the urine was collected by timed specimens in bottles containing 10% hydrochloric acid as a preservative and kept in a refrigerator until determinations were made. It was found that urines must be at a *p*H approximating 3 to give maximum accuracy on the rabbit aorta test.[25] Clinitests were done on each urine sample as well as Sjoerdsma's qualitative determination of 5-hydroxyindolacetic acid (5-HIAA).[26] Amino acid excretion studies by 2-dimensional chromatograms were run on a few appropriate samples.

The patients were all seen and examined personally by the author at the University of Chicago Clinics or at Manteno State Hospital, but not all were hospitalized. The clinical distribution of cases is indicated in Table 2. None of the patients was pregnant or suffering from acute anxiety. Except for the 6 patients with Wilson's disease, none had cirrhosis and only 1 was receiving tranquilizing drugs. All of 10 patients with a constant blood pressure level above 140/90 mm. Hg were in the parkinsonism group. As far as possible, repeat specimens were obtained and, in patients hospitalized, daily collections were aimed for. Except in the latter group, it was unfortunately impossible to restrict the use of medication other than tranquilizers. A total of 48 patients with clinically demonstrable basal ganglia involvement were studied by one or the other method; 126 controls were tested with Simola's reaction and 238 with the bioassay.

RESULTS

The colorimetric study was done on a total of 234 urine samples, 68 of which proved to be positive. When these were divided into cases with and without involuntary movements (Table 1), it was found that the former had an average of 59.6% positive as opposed to 2.3% for the latter. The 3 positive results in the control group were 1 case of Freidreich's ataxia and 2 of cirrhosis of the liver.

Similar results were obtained with the bioassay of the 44 patients tested, 24 being positive (54.5%) (Table 2). This can be compared with the 6 to 18% positive reactions in large

TABLE 2

Disease	Rabbit aorta Number	Positive	In common	Simola Number	Positive
Parkinson's					
Postencephalitic	8	4	5	6	2
Idiopathic or "arteriosclerotic"	15	6	12	12	3
Drug induced	1	1	0	0	0
Choreoathetosis	4	1	1	2	1
Dystonia musculorum	3	1	0	0	0
Wilson's disease	4	4	4	6	6
Huntington's chorea	5	5	5	5	5
Chorea—Sydenham's	2	0	0	0	0
Congenital	1	1	0	0	0
Senile	0	0	0	1	1
Degenerative brain disease	1	1	0	0	0
Totals	44	24	27	32	18

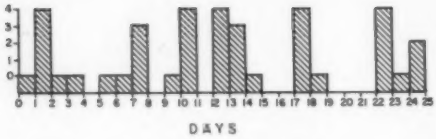

Fig. 1. Determinations of urinary pressor substances by Simola's reaction in a case of Wilson's disease. A scale of + to ++++ has been established, depending on the intensity of the color reaction. This figure demonstrates intermittent positivity.

groups of hypertensive patients and normal controls obtained by Helmer,[24] McMillan,[27] von Euler,[28] and ourselves.[29] In some of our positive cases in the study group, the contraction obtained was as high as the equivalent of 1,000 to 2,000 μg. norepinephrine excretion per day, or well within the range found in pheochromocytoma.[30] The highest positive groups appear to be the ones with Wilson's disease and Huntington's chorea. It is noteworthy that these are the groups with the highest family incidence.

Other studies were also done on the urine of our patients. Because of the known incidence

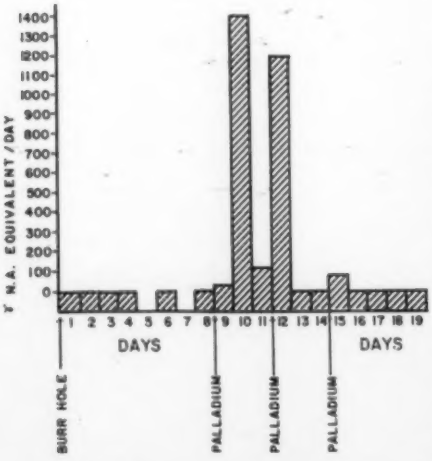

Fig. 2. Effect of placement of palladium beads in the globus pallidus of a patient with Parkinson's disease. The method used in this experiment is the bioassay on a strip of rabbit aorta (Helmer).

of false-positive reactions in diabetes,[25,31] clinitests were done on the urines of the 48 patients and were all negative. Sjoerdsma's qualitative reaction[26] for a 5-HIAA was also negative in all cases, indicating that serotonin or its derivatives were probably not involved in the positive reactions; 2 gm. of tryptophan given by mouth to 1 patient with Wilson's disease who had been intermittently positive did not produce a positive reaction on the three days following the test ingestion. Amino acid excretion of the 6 patients with Wilson's disease was fairly constant and showed no correlation with the results of the present study.

In a few patients, consecutive determinations over a period of ten to twenty days showed considerable variation in positivity from day to day (Fig. 1). This was particularly true for choreoathetosis and Wilson's disease. On the other hand, consecutive determinations on 3 healthy persons, not included in the original control group, over periods of ninety, forty, and twenty-five days, respectively, with the Simola reaction were consistently negative.

Stereotaxic operations were performed on 2 patients with Parkinson's disease who had previously been negative (Fig. 2). On the days following the placement of the radioactive palladium in the globus pallidus in 1 patient and the posterior thalamus in the other, the excretion of the unknown substance rose to very high levels; 2 other patients with craniotomies but with no basal ganglia disease served as controls. Of these, 1 had a meningioma removed from the region of the sella turcica, the other a sarcoid granuloma removed from near the third ventricle. Although the operative stress was at least as great as for the chemopallidectomies, there was no detectable increase in excretion of our unknown substance.

The contractions obtained on the aorta strip with the urines of several positive cases were completely abolished or greatly reduced when Regitine was added to the bath with the urines (Fig. 3). Only occasionally, a very small portion of the original contraction was still present after Regitine.

DISCUSSION

In view of these findings, 3 main questions must be answered: Are we dealing with a

significant change? If so, what substance is involved, and, finally, what is its physiologic meaning, if any?

As to the first question, it appears from our data that there is in the urine of 50 to 60% of patients with undoubted organic disease of the basal ganglia a substance of unknown nature having the property of contracting a strip of rabbit aorta and of giving a positive Simola reaction. Although it is agreed that both of the methods used in this study are, to a certain degree, unspecific and that false-positive reactions are known to occur in their use,[22,24] nevertheless, the incidence of positive results in our series of patients is sufficiently high to indicate a significant specific relationship. This incidence is at least 3 times greater than that of false-positive reactions in our own control material or that reported by other workers. Such a proportion of positive responses has not been found in any other group of patients tested, except those with pheochromocytoma. Anxiety,[32] diabetes,[31] or cirrhosis[25] were not factors in our patients, and only a small number of the patients showing positive reactions (4 of 27) had permanent elevation of blood pressure. The magnitude of the bioassay response in some of the patients and the invariable concordance of the bioassay and the Simola test in those patients for whom both were used also suggest that our findings are meaningful.

To elucidate the nature of this substance, we tested a number of products known to be present naturally or artificially in the urine (Table 3). Only a few of the substances tested were positive in Simola's reaction and also produced a contraction of the aorta strip. Other substances such as metanephrine, normetanephrine,[33] kallidin,[24] 3, 4-dehydroxyphenylacetic acid,[27] N-methyl serotonin, and bufotenin, also known to be in the urine, were not available for study. It is evident that the group giving positive results by both methods includes all the catecholamines. Serotonin and its derivatives are almost certainly eliminated by our negative 5-HIAA dosage and by the tryptophan experiment. The Regitine effect upon the positive urines would also seem to rule out kallidin, histamine, and angiotonin. With the methods used, it is impossible to say which of epinephrine, norepinephrine, dopamine, or the meta-derivatives is involved. Because of the lack of marked hypertension (sustained or paroxysmal) in the patients studied, we are inclined to believe that the greatest part of the contraction is not the result of epinephrine or norepinephrine. Recent studies with dopamine indicate that it is more than a simple precursor of norepinephrine and that it probably has a physiologic function of its own.[12,34] Like norepinephrine and serotonin, it can be depleted from the brain by an injection of reserpine.[12] Moreover, it is known

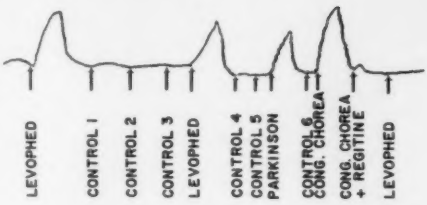

Fig. 3. Copy of the "waxed paper" strip of experiment A-35, showing the contractions obtained with the urines of a case of Parkinson's disease and a case of congenital chorea. The latter urine was then reinjected with Regitine, and most of the contraction was abolished.

TABLE 3

Substance tested	*Positive Simola*	*Positive contraction*
Histidine	No	—
Histamine	No	Yes
Growth gonadotropin	No	—
Chorionic gonadotropin	No	—
ACTH	No	—
Pregnandiol	No	—
Estrogens	No	—
Testosterone	No	—
Pitressin	No	—
Adrenal cortex	No	—
Tyrosine	No	—
Angiotonin	No	—
Serotonin	No	Yes
Epinephrine	Yes	Yes
Norepinephrine	Yes	Yes
Isopropylarterenol	Yes	—
Catechol	Yes	—
Dopamine	Yes	Yes
Epinine	Yes	Yes

to be in high concentration in the basal ganglia[13] and is only about one-fiftieth as active as norepinephrine on the blood vessels.[28]

Only chemical studies, now under way, can demonstrate whether the substance in question is actually present and, if so, whether it is a catecholamine. Should this be the case, it is interesting to speculate on the possible role and origin of a catecholamine found in this clinical setting. It seems clear that the symptoms of the disease are not themselves the basis for this metabolic deviation, because patients with negative results in the urine may exhibit as much tremor and rigidity as those giving positive reactions. It is possible that the brain lesions of the diseases produce the substance, as the radiopallidectomy results perhaps suggest. Or it may be that an enzymatic defect in the liver leads to a failure of metabolism of the substance and its accumulation in the circulation with toxic damage to the neurons of the basal ganglia.

While this report can be only tentative in view of the limitations of the methods we have been obliged to use, we believe that the results of our work are suggestive enough to warrant reporting and to serve as a point of departure for more definitive chemical studies.

SUMMARY

From recent observations on the production of Parkinson-like syndromes by various "tranquilizers" and ganglion blocking agents and from studies on the distribution of norepinephrine, serotonin, and dopamine in the brain and on the depletion of these substances by reserpine and chlorpromazine, the working hypothesis was formulated that a disorder of catecholamine metabolism may possibly be found in basal ganglia diseases. In order to test this hypothesis, urines of patients were assayed for pressor response with a modification of the rabbit aorta test of Helmer, Sjoerdsma's qualitative determination of 5-HIAA, and Simola's iodine reaction.

The results on more than 40 cases (including examples of Parkinson's disease, Sydenham's chorea, congenital chorea, Huntington's chorea, choreoathetosis, dystonia musculorum deformans, Wilson's disease, and drug-induced parkinsonism) indicate that there is a statistically significant increase in the urine of most of these patients of a substance having pressor action on the rabbit aorta strip and turning purple or red when heated in the presence of iodine (Simola's reaction). The pressor reaction obtained was always marked and sometimes was in the range expected from pheochromocytoma. At no time did Sjoerdsma's qualitative reaction become positive, indicating the substance studied was not serotonin or its urinary derivative, 5-HIAA.

Chemopallidectomy with radioactive palladium in parkinsonian patients released extremely high amounts of this substance in the urine, while similar operations in other regions of the brain did not do so.

Thus, the results of this study indicate that a metabolic abnormality is present in a wide variety of basal ganglia diseases. The nature of this abnormality is still indefinite, but it appears to be related to the metabolism of catecholamines. The physiologic and clinical implications are being investigated.

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The central nervous system in congenital heart disease

Maynard M. Cohen, M.D.

THE RECENT successful application of open heart surgery to patients with congenital heart disease has necessitated a reevaluation of nervous system changes in patients with cardiac anomalies. It has become essential to determine if preexisting neural lesions may decrease the probability of surgical success or may affect the future life of patients with successful correction of the cardiac defect. Possible damage consequent to the operative procedure must also be evaluated.

Although neurologic findings have long been recognized as frequent concomitants of congenital heart disease, a paucity of information exists concerning the variety of neural lesions responsible for the clinical symptomatology. The literature has been concerned primarily with cerebrovascular accidents and with intracranial abscesses. Little is known of other forms of nervous system involvement and detailed neuropathologic studies have yet to be reported.

The following report surveys the neuropathologic changes in 100 fatal cases of congenital heart disease. Subsequent communications will be concerned with clinical and physiologic aspects of nervous system involvement in congenital heart disease and their pathologic correlates.

MATERIALS AND METHODS

Between April 1, 1956, and April 1, 1957, 100 cases of congenital heart disease came to autopsy at the University of Minnesota Hospitals. Sixty deaths followed surgical procedures, and the remaining 40 died without any operative intervention. In virtually all surgical cases, the operative procedure involved a direct intracardiac approach. Circulation was maintained extracorporeally by perfusion with a DeWall oxygenator. The perfusion period approximated twenty minutes, during which time the oxygen delivered to the body circulation was estimated to vary from one-fourth to one-half of the normal resting level.

In all fatal cases, the brain was removed as quickly as possible after death and fixed in 10% formalin solution. Following fixation for eight to fourteen days, the brains were examined carefully externally and sectioned. Blocks for microscopic examination were taken routinely from the frontal, parietal, temporal, and occipital cortex and white matter, basal nuclei, internal capsule, hippocampus, thalamus, hypothalamus, pons, medulla, cerebellum, and cervical spinal cord. Additional sections were taken from any area suggesting gross pathology. The sections were then stained with hematoxylin and eosin, Weil, and Nissl thionine. Where indicated, Sudan stain for fat and Bielschowsky and Mallory phosphotungstic acid hematoxylin methods were also employed.

RESULTS AND DISCUSSION

The age distribution of the cases studied is listed in Table 1.

In virtually all cases, cerebral congestion was severe and petechiae were common, particularly in the floor of the fourth ventricle and hypothalmus, in areas where petechiae often appear on an agonal basis. These findings may be related to the heparinization necessary to the perfusion procedure and to the vascular damage resulting from lower oxygen tension during use of the mechanical oxygenator.

From the Division of Neurology, University of Minnesota Hospitals.

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In addition to congestion and petechiae, 75% of the surgical cases and 65% of the nonsurgical cases exhibited other significant pathologic changes as summarized in Table 2.

Alterations related to acute vascular insufficiency. This group includes recent encephalomalacia, diffuse cortical necrosis, and focal necrosis arising from acute anoxia. There were also 2 cases of multiple small cerebral hemorrhages. These were considered to arise consequent to the hypoxia during surgery, damaging the walls of the small vessels together with heparinization necessary for the perfusion. Acute encephalomalacia was observed in both surgical and nonsurgical cases. Acute encephalomalacia was evident in 2 different patterns. The first was the classical pattern of fragmentation of tissue with phagocytes and often with petechial extravasation of blood. The second, more acute form, was of patchy demyelination with few or no phagocytes. Focal necrosis was observed only in the surgical cases. The lesion consisted of a small zone of coagulation necrosis about a central capillary with peripheral demyelination (Fig. 1). Diffuse cortical necrosis of the classical pattern was present in only 1 case in the surgical group. Old encephalomalacia was included in the group of acute changes, since it represented an acute infarction occurring some time in the past.

Findings indicative of recent vascular insufficiency were present in 14, or 23%, of the surgical cases. An additional 25% of surgical patients died within twenty-four hours after the operative procedure. Some of these might have demonstrated destructive lesions had they survived sufficient time to allow full development of the histologic changes. In only 3 cases, or 21% of those dying with evidence of acute cerebrovascular insufficiency, was there old encephalomalacia, focal gliosis, or other degenerative changes which might suggest predeliction to an acute vascular accident.

The most extensive pathologic study of the nervous system previously reported is that of Berthrong and Sabiston.[1] They noted that cerebral infarction occurred in 25 of 135 patients with cyanotic heart disease. Nineteen represented infarcts of recent origin, and 15 of these patients died following surgery. These investigators believed that the infarcts were generally produced by thrombi or emboli. Cardiac failure was considered to have little effect on the genesis of the lesion.

TABLE 1
CONGENITAL HEART DISEASE
AGE DISTRIBUTION (100 CASES)

	Postsurgical fatalities	*Nonsurgical fatalities*
0 to 3 months	7	20
4 to 6 months	3	11
7 to 12 months	5	5
1 to 4 years	21	1
5 to 10 years	14	0
11 to 20 years	9	1
Over 21 years	1	2
Total	60	40

The present study together with previous investigations suggests that the inability of the circulation to deliver oxygen and adequate nutrients to the brain is responsible for the infarction, and specific occlusion rarely occurs. It has been adequately demonstrated that areas of vascular occlusion are commonly absent in cases of infarction.[2] In addition, the studies of Wilson and associates[3] emphasize the role of cardiac failure in the genesis of the cerebral infarction. In the investigation now reported, the diminution of circulation during the period of surgery and mechanical perfusion appears

TABLE 2
NEUROPATHOLOGIC FINDINGS IN 100 CASES OF CONGENITAL HEART DISEASE

	Surgical		*Nonsurgical*	
	No.	*%*	*No.*	*%*
ACUTE ANOXIC EPISODES				
Recent encephalomalacia	4	6.7	6	15
Old encephalomalacia	4	6.7	5	12.5
Diffuse cortical necrosis	1	1.7	–	–
Cerebral hemorrhage	2	3.3	–	–
Focal necrosis	7	11.7	–	–
CHRONIC ANOXIA				
Focal demyelination and gliosis	6	10	4	10
Meningeal thickening	8	13.3	3	7.5
Calcification	4	6.7	4	10
SUPPURATIVE PHENOMENA				
Solitary cerebral abscess	–	–	2	7.5
Multiple cerebral abscess	1	1.7	–	–
ASSOCIATED ANOMALIES				
Telangiectasis	7	11.7	4	10
Hydrocephalus	1	1.7	–	–
Mongolism	–	–	2	5
OTHER				
Diffuse demyelination and gliosis	3	5	3	7.5
Pontine spongiosis	10	16.7	7	17.5

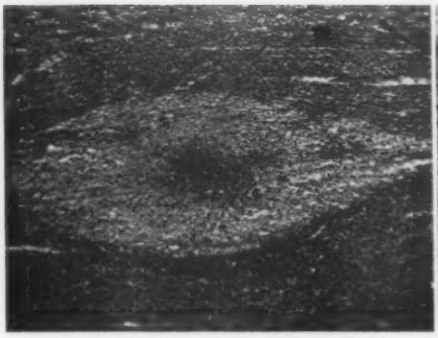

Fig. 1. Focal necrosis. Small zone of coagulation necrosis with surrounding demyelination

Fig. 2
Calcium deposition in basal ganglia

of major consequence in the genesis of the cerebral infarction and in focal necroses.

In the present series, neuronal involvement was minimal or equivocal. Involvement of cortical neurones has been reported by Courville[4] in a newborn exhibiting severe cardiac malformation with consequent profound disturbance of the circulation. The infant survived twenty-four days but exhibited focal and laminar necrosis of the cerebral cortex comparable to that observed in severe anoxia of thirty-six to seventy-two hours' duration. This author then suggested that the pathologic change was a product of the duration of anoxia and the degree of oxygen want, and that lesser degrees of anoxia over a longer period could produce the same alterations as acute severe anoxia over a shorter time.

Alterations secondary to chronic hypoxia. This group includes perivascular demyelination and gliosis, meningeal thickening, and calcification often in association with ferrugination. The small areas of focal demyelination and gliosis (10% of all cases) were generally perivascular and identical to those often observed when arteriosclerosis produces a similar chronic deficiency in cerebral oxygen supply.

Meningeal thickening was also considered to arise as a result of chronic oxygen lack. The majority of the 11 patients exhibited thickening of the meninges with fibrous connective tissue. However, in some, there was also infiltration with small numbers of phagocytes and mononuclear leukocytes. Similar meningeal fibrosis was reported by Courville[4] in a newborn with congenital heart disease.

Deposition of calcium in preexisting tissue is generally considered to be a degenerative phenomenon related to inadequate oxygenation or nutrition.[5] The calcification observed was variable and was distributed in 4 different patterns: [1] deposition in basal ganglia, particularly in perivascular location (Fig. 2), [2] deposition on neurones or glial cells, [3] scattered throughout areas of severe gliosis and demyelination, and [4] in the thickened fibrotic meninges. Calcification was present in patients varying in age from 1 month to 10 years. Half of the 8 patients exhibiting this alteration were under the age of 2 months, thus suggesting an intrauterine deficiency of vascular supply.

No instances of similar calcification were found in the literature. However, in Bochnik's[6] report of the autopsy findings in 6 cases of cyanotic congenital heart disease, he noted pseudocalcinosis in 1 case. Prominent corpora amylacea were also present in 2 of his patients aged 5 and 23 years. Isomorphic gliosis was present in the central white matter of all patients in whom the cardiac involvement was of increasing intensity.

Suppurative phenomena. Suppuration was observed in the pattern already described by a number of investigators.[7,8] Two cases of brain abscess appeared in the nonsurgical

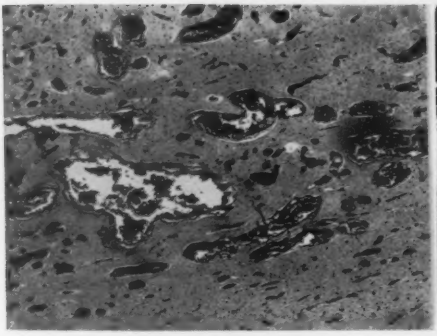

Fig. 3
Arteriovenous malformation

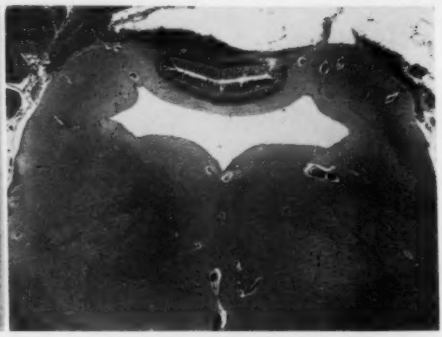

Fig. 4. Bilateral symmetric spongiosis in reticular formation of pons

group, or in 5%. In 1 instance, multiple brain abscesses followed embolic phenomena secondary to postsurgical bacterial endocarditis.

The association of cerebral abscesses with congenital heart anomalies has been adequately described in the literature. The incidence in nonsurgical cases in this series is in accord with the 4 to 6% recorded in the literature.[7] Abscesses have been postulated to occur as a result of infected venous thrombi breaking loose and passing through the cardiac defect to lodge in the cerebral circulation. However, a more commonly held theory suggests that bacteria normally in the venous blood are not filtered out by passage through the lungs and may reach the central nervous system. Abscess formation under these circumstances may be abetted by diminution of cerebral oxygen tension or the possibility of an infarction preceding the arrival of the infected blood.

Other developmental anomalies. Additional developmental anomalies commonly accompanied the cardiac defect. Mongolism was present in 2 instances and hydrocephalus in 1. However, the most commonly associated abnormality was vascular malformation of the nervous system. This occurred in the form of telangiectasis in 11% of all cases. In some telangiectatic lesions, occasional larger vessels were associated with the capillary lesion. This incidence is considerably in excess of the approximately 1% in the general population,[9] but the exact assessment of the increase is difficult. The careful selection of multiple sections would bring to light more cases of telangiectasis. In addition, the extreme congestion and dilation of all vessels following congestive failure made dilated vessels more evident visually and, thus, more readily sectioned. However, the marked increased incidence and the presence of larger than capillary vessels in these lesions (Fig. 3) indicated that increased association of cerebrovascular anomalies with cardiac anomalies was valid.

Bochnik[6] reported on the neuropathologic findings of 6 cases of cyanotic congenital heart disease and was impressed by the vascular changes in the brain. He noted ectasia of the vessels with increased tortuosity to the point of racemose hemangioma formation. He observed fibrotic changes in all vessels and some arterial thrombi. There was necrosis under the pial convolutions related to vessels, which he considered resembled that observed in Sturge-Weber disease. He also noted plasma transudates, cerebral edema, and isomorphic gliosis in the central white matter.

Involvement of additional systems in congenital heart disease is commonly recognized. Richards and associates[10] reported associated malformations in 36% of 50 cases of proved congenital heart disease in 6,053 newborn infants. In 100 neonatal autopsies on cases of congenital heart disease, Ober and Moore[11] reported that 7 had severe anomalies of other systems. In 3, the concomitant involvement

was of the nervous system. McMahon and associates[12] reported some associated developmental alteration in 21% of 488 cases of congenital heart disease. The central nervous system or organs of special senses were involved in 10 cases. Wiland[13] noted extracardiac anomalies in 57 of 200 consecutive autopsied cases of congenital heart disease. Hydrocephalus was present in 2 cases. Conversely, the incidence of congenital heart disease among mental defectives has been reported to be 7 times that of the general population.[14] Mongolism is particularly associated with congenital heart disease.[10,12,13,15]

Other lesions. In the remaining group, the relationship of the nervous system pathology to the cardiac involvement could not be readily determined. Six per cent of all cases exhibited diffuse demyelination and gliosis. In some cases, the lesions could not be histologically distinguished from diffuse sclerosis. The involvement was generally limited to the white matter, with sparing of the U fibers and of the cerebellum. Half of the cases observed were in infants under 6 months of age, indicating an intrauterine origin. Several possibilities exist for this association. Both the cardiac anomaly and the diffuse gliosis may be due to a common stimulus appearing during development, which may be on a genetic basis or may arise from the fetal environment. It is also possible that oxygen deficiency due to the cardiac defect may produce the diffuse nervous system involvement. Further studies are being carried out to more accurately delineate the causal factors.

The final finding remains to be evaluated. This consisted of a symmetrical spongiosis of the reticular formation in the pons (Fig. 4) without visible rostral or caudal extension. Neuronal involvement was not evident. It occurred in 17% of the cases with equal implication in both the surgical and nonsurgical groups. The alteration occurred almost entirely in children, the oldest of whom was 19 months. Free fat was not noted in the Sudan stains. The possibility exists that this finding is an artifact and does not represent true pathologic alteration. However, the young ages of the patients and repeated symmetry of the lesions suggest a pathologic basis. Further studies are under way to clarify this finding.

SUMMARY

A neuropathologic study of 100 fatal cases of congenital heart disease revealed that severe congestion or petechia was almost uniformly present in all cases.

Focal necrosis was the single central nervous system finding limited to the operative group. Acute encephalomalacia occurred in both groups. In surgical cases, these acute anoxic episodes appeared to be related to inadequate cerebral oxygenation during the operative procedure.

The remaining findings were common to both groups and included: patchy demyelination and gliosis, meningeal thickening, cerebral calcification, suppurative phenomena, cerebral telangiectasis, additional developmental anomalies, diffuse gliosis, and spongiosis of the pontine reticular formation.

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Immunochemical studies on muscle proteins

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IMMUNOLOGIC STUDIES on structure proteins of muscle may be expected to contribute to both the knowledge of the organization of these proteins and also the understanding of basic immunologic mechanisms. The immunologic approach offers specificity and sensitivity in technics. Muscle proteins such as myosin, actin, and tropomyosin provide purified material well characterized by independent investigations. These experimental advantages can be favorably combined with the conceptual attractiveness of studying the immunologic properties of intracellular structure proteins as a class, contrasted to surface antigens on the one hand and to intracellular soluble proteins on the other. Previous work has resulted in interesting findings, such as the isoantigenic nature of actin,[1,2] the lack of species specificity of myosin,[3] and additional evidence of the relationship between myosin and tropomyosin A.[2]

This communication describes some experiments on tropomyosin A and myosin which are necessary to permit subsequent detailed quantitative study. The results presented here seem to be consistent with current concepts of the complex structure of myosin and with the experimental evidence pointing to its relation to tropomyosin A.

MATERIAL AND METHODS

Protein preparations. Myosin was prepared from the muscles of cats and rabbits according to the method of Szent-Györgyi.[4] Heavy impurities were removed by high speed centrifugation for one hour at 35,000 × g. Tropomyosin A was prepared from the adductor muscles of the clam (Venus mercenaria) according to Laki[5] and from rabbit myosin according to Kominz and associates[6] by treatment with copper cyanide followed by ammonium sulfate fractionation and dialysis. Tropomyosin B was prepared from rabbit muscle according to Bailey.[7]

Immunization of rabbits. Rabbits were immunized intravenously with one of the antigens mentioned without the use of adjuvants. Each antigen was assigned to a group of 3 to 5 rabbits. Each rabbit received 6 injections of 10 mg. of protein in 1-cc. volume on alternate days and was bled five to seven days after the last injection. If more serum was needed, another set of 6 injections was given later and the same schedule followed. The rabbits were bled from the ear vein, and sera were passed through Seitz filters before use.

Quantitative precipitin reactions. Sera were tested individually rather than pooled. Sera of rabbits immunized with cat myosin or clam tropomyosin A were tested undiluted. Sera of rabbits immunized with rabbit muscle proteins were tested both undiluted and in dilutions. Graded quantities of antigens were added to establish optimal ratios. The antigen dilutions were usually made in buffered 0.5 M sodium chloride, since myosin and clam tropomyosin A would precipitate at physiologic salt concentrations. An equal volume of serum was added to the antigen dilutions, so that the final salt concentration was 0.32 M. All antigens remained in solution at this salt concentration in normal rabbit serum.

Seitz filtration of the antigens was not always possible due to the high viscosity of these proteins in solution. Such preparations were centrifuged at high speed for one hour, and

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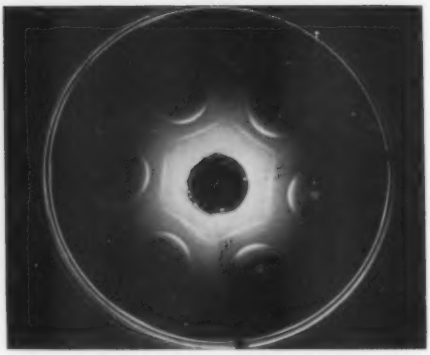

Fig. 1. Agar diffusion. Anti-clam tropomyosin A serum vs. clam tropomyosin A. Serum is in center well. Well at 3 o'clock contains 5 mg. per cubic centimeter of antigen. The others in clockwise order: 2.5, 1.25, 0.62, 0.31, and 0.16 mg. per cubic centimeter of antigen. Note precipitation in lines forming hexagonal pattern. See text.

the top layer of the supernatant was used in tests. Since the preparation of antigens involves either treatment with organic solvents or extensive and abrupt *p*H and osmotic changes, this precaution seemed to be sufficient to insure sterility, as evidenced by the low precipitated nitrogen in the controls.

Tests were set up at room temperature and then incubated for a week at 0° C. Exposure to higher temperatures was avoided because of the danger of irreversible changes of the antigens. Precipitation was usually slow. While some precipitate usually formed overnight, even the fastest reacting system—clam tropomyosin A with its specific antiserum—required four to five days for complete precipitation.

The amount of precipitated protein was estimated by two independent methods. The first followed the procedure of Kabat and Mayer,[8] except that the nitrogen of the washed precipitates was determined by direct nesslerization. With this method, the supernatants were further utilized for verification of the equivalence points and for other experiments described under Results.

The other procedure was described by us recently.[9] This depends on paper chromatographic separation of the antigen-antibody precipitate from the proteins of the supernatant and determination of the precipitated proteins by spectrophotometric measurement of the brom-phenol blue bound by these proteins under carefully standardized conditions.

In another series, paper electrophoretic analysis of the antigen-antiserum mixtures was carried out at low current intensities—0.3 ma.—to minimize heating heating effects. Detailed description of this experiment appears under Results.

Agar diffusion experiments were performed by the Ouchterlony technic,[10] in 1% agar dissolved in 0.4 M sodium chloride to 0.01 M sodium phosphate buffer at *p*H 7; ⅛-in. diameter wells ½-in. apart formed a hexagonal pattern around the central well. Usually, 0.5 cc. of undiluted serum and 0.5 cc. of antigen in the 0.16- to 10-mg. protein per cubic centimeter concentration range were used. To avoid artifacts, the wells were not refilled. The plates were incubated at 0° C. and evaluated in the cold room to avoid temperature changes. With some sera, the lines of precipitate appeared in three days. Some weaker sera showed lines only after several weeks.

RESULTS

Section 1. Anti-clam tropomyosin A serum and clam tropomyosin A. According to the schedule described, 3 rabbits were immunized with clam tropomyosin A. All 3 sera gave immediate precipitates with clam tropomyosin A, but the amount of precipitated nitrogen was found to be greater after five days' incubation than the amount determined on the third day. In the agar diffusion experiments, the undiluted serum gave strong lines with 0.6 to 5 mg. protein per cubic centimeter of clam tropomyosin A in about seventy-two hours at room temperature, while the same antigen at 0.16 and 0.32 mg. per cubic centimeter concentration showed lines only at eighty hours. A duplicate plate incubated in the cold started to show precipitin lines after five days. The intensity of the lines showed an increase with prolonged incubation. The photograph shown in Figure 1 was taken after eight days in the cold, and no material change was observed during the three weeks' additional observation. As can be seen, the lines are slightly curved, the convexity being toward the well contain-

ing the antigen, and the line is closer to the well containing the lower concentrations of antigen. Even after prolonged observation, only a single line could be discerned with all concentrations of antigen studied.

The agar plate reproduced in Figure 1 permits some rough measure of the purity of the clam tropomyosin A preparation. The lowest concentration of antigen, 0.16 mg. per cubic centimeter, still gave a distinct line. It may be thought, therefore, that a contaminating minor component in a similar concentration would have shown up with the highest concentration of antigen studied in form of a second line. The single line observed would indicate less than 3% impurity by this criterion.

Quantitative precipitin reactions were carried out by adding increasing quantities of antigen, from 7.3 to 117 μg. of nitrogen, to 1-cc. samples of undiluted anti-clam tropomyosin A serum. Actually, the precipitates observed were large enough so that only 0.5 cc. of serum and half of the aforementioned quantities of the antigen were necessary. After a week's incubation in the cold, the nitrogen content of the washed precipitates was estimated by nesslerization and the chromatographic method. As indicated in Figure 2, the results obtained by the 2 methods are in close agreement. The serum used in this series was intermediate in strength, being about midway between the strongest and weakest obtained. It is apparent that larger quantities of precipitates are formed with increasing quantities of antigen added until an optimum is reached, at about 70 μg. in this experiment, beyond which the excess of antigen exerted an inhibitory effect. Testing one half of the supernatant with further addition of antiserum and the other half with more antigen, little or no excess of either was found at or near the maximum of the curve, whereas these tests indicated antigen in excess near the upper limits and antibody excess at the lower limits of the range shown. These findings justify the assumption that all the antigen added is precipitated at the maximum, and the nitrogen precipitated above this quantity is antibody nitrogen. The antibody concentration of the 3 sera studied was calculated this way to be 144, 228, and 492 μg. antibody nitrogen per 1 cc., respectively. At the equivalence point

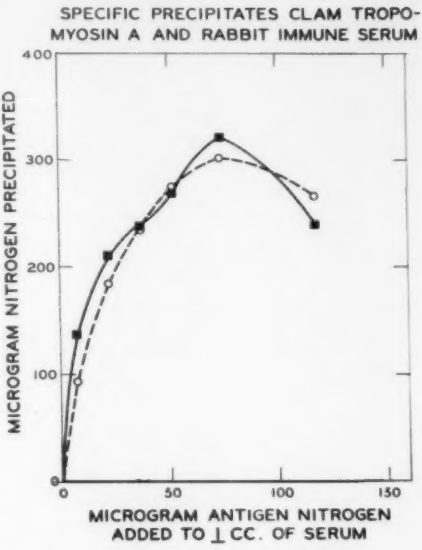

Fig. 2. Specific precipitates: Clam tropomyosin A and anti-clam tropomyosin A rabbit serum. Open circles: precipitate estimated by nesslerization; solid squares: precipitate estimated by paper chromatographic technic

indicated by the supernatant tests, the ratio of antigen nitrogen to antibody nitrogen was found to be 5.5, 5.7, and 6.7 antibody nitrogen to 1 antigen nitrogen. If the molecular weight of tropomyosin is 50,000 and the antibody is a 150,000 molecular weight gamma globulin, a 1:6 nitrogen ratio would indicate that 2 antibody molecules react with 1 molecule of tropomyosin under the conditions specified. In the antibody excess region, however, precipitates were formed which contained 12 to 13 times as much antibody nitrogen as antigen nitrogen. This suggests that the tropomyosin molecule is capable of reacting with 4 antibody molecules.

The gamma globulin nature of the anti-clam tropomyosin A antibody is demonstrated in Figure 3. Clam tropomyosin A in the amount of 0.01 cc. was applied to the top strip, and 0.01 cc. of anti-clam tropomyosin A serum was applied to the middle strip. A mixture of the antigen and antiserum was applied to the

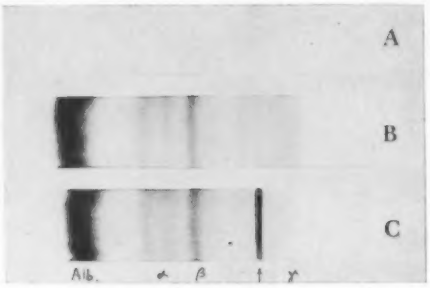

Fig. 3. Paper electrophoresis. (*A*) Clam tropomyosin A alone. (*B*) Anti-clam tropomyosin A serum alone. (*C*) Mixture of anti-clam tropomyosin A and clam tropomyosin A. Arrow indicates point of application.

bottom strip. All 3 strips were subjected to electrophoresis and stained with brom-phenol blue. The presence of the precipitate in the third strip is conspicuous. Furthermore, comparison of the second and third strips shows that the gamma globulin fraction is diminished in the third strip, while all the other serum components show the same distribution and intensity as in the second strip containing the serum alone.

Section 2. Anti-cat myosin serum and cat myosin. In all, 4 rabbits were immunized with myosin prepared from cat muscles. When these sera were tested at the end of the first series of injections, after the first bleeding, none of them appeared to react in the agar diffusion experiments and very small quantities of precipitates formed in quantitative precipitin tests. These animals were therefore given another series of 6 injections. Sera from this second bleeding showed precipitin lines in the agar after about a week's incubation in the cold. The amounts of precipitate obtained when graded quantities of myosin were added to samples of the serum showed only a slight increase, however. In addition, there were large differences among the 4 sera, as shown in Figure 4. The complexity of this system is also apparent from the discrepancy between the quantitative precipitin reactions and the agar diffusion experiments carried out with the sera from the second bleeding. The 2 sera, A and D, which gave distinct lines after one week's incubation in the cold were photographed ten days after the start of the incubation, and the appearance of the reaction is reproduced in Figure 5. It is apparent that there are several lines of precipitate with both sera, which may be indicative of the complex antigenic nature of myosin in contrast to its apparent physicochemical homogeneity under conventional experimental conditions. It should be noted that serum D gave the largest amounts of precipitate (Fig. 4) but that serum A, which gave almost as good lines in the agar, gave much smaller precipitates. Conversely, serum B, which was almost as good as serum D in the quantitative experiment, gave the merest indication of a precipitin line in the agar after only three weeks' incubation. As shown in Figure 4, the amount of precipitate obtained with serum D exceeds the antigen nitrogen added for the lower concentrations of the latter only, where supernatant tests indicate antibody excess. In view of the apparent multiplicity of this system, quantitative evaluation of the precipitin

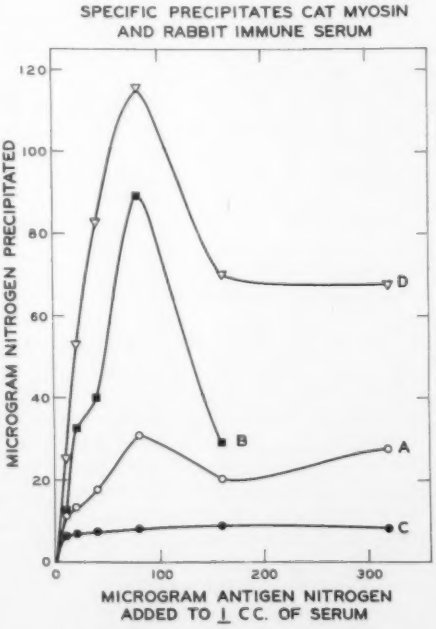

Fig. 4. Specific precipitates: cat myosin and anti-cat myosin rabbit serum. Lines A, B, C, and D represent sera of 4 different rabbits.

Fig. 5. Agar diffusion: anti-cat myosin sera A and D vs. cat myosin M. Note precipitation in multiple vertical lines. See text.

curves would be meaningless. The only statement permissible would be that serum D contains not less, but probably more, than 40 μg. of precipitable antibody per cubic centimeter.

Section 3. Cross reactions of anti-clam tropomyosin A and anti-cat myosin sera. It was reported earlier[2] that anti-clam tropomyosin A sera precipitated mammalian myosins and that clam tropomyosin A was precipitated by anti-myosin sera. In the present study, quantitative evaluation of these reactions was attempted.

Reaction of anti-clam tropomyosin A sera with cat myosin. The sera characterized in Section 1 were set up against graded quantities of cat myosin. As may be seen from Figure 6, the amount of precipitate formed generally increased with the amount of myosin added. The supernatants were tested with the quantity of clam tropomyosin known to give maximal precipitate with the anti-clam tropomyosin A serum. The amount of precipitate formed in these supernatant tests contained only about one half of the antibody of the sera before the reaction with cat myosin. The amount of antibody precipitated in these supernatant tests tended to decrease with the increase of precipitates formed previously with cat myosin.

In another experiment, the optimal amount of clam tropomyosin A was added to the anti-clam tropomyosin A sera in order to remove all the antibodies from this protein. The supernatant was tested against clam tropomyosin A to verify the complete absorption. The sera so treated failed to precipitate cat myosin altogether.

From the cross reaction of the anti-clam tropomyosin A serum with cat myosin, the data permitted an estimation of the degree of crossover. The supernatants gave precipitates with clam tropomyosin A added, but these precipitates contained only half the antibody known to be originally present in the serum. The other half must have reacted with the cat myosin. The precipitin curve in Figure 6 fails to show a distinct maximum, however, and it may be thought that, under more suitable conditions, more of the antibodies would have reacted. The finding that absorption with clam tropomyosin A abolishes the reaction with cat myosin altogether, as well as the single line seen in the homologous system (Fig. 1), argue against the possibility that there would be 2 types of antibody in the serum. It may be concluded that the degree of crossover is not less than 50% between the clam tropomyosin A and cat myosin. This means that, from 100 antibody molecules directed against clam tropomyosin A, at least 50 are capable of reacting with cat myosin. A 50% crossover is a fairly high figure compared to other systems studied,[8] and, as pointed out before, this probably is a minimum estimate.

Reaction of anti-cat myosin sera with clam tropomyosin A. Graded quantities of clam tropomyosin A were added to samples of the anti-cat myosin sera. Small but significant

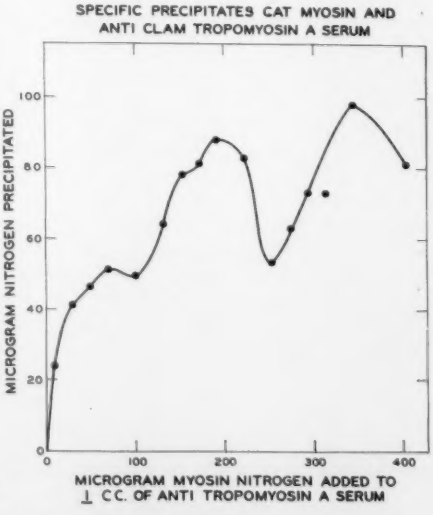

Fig. 6. Specific precipitates: cat myosin vs. anti-clam tropomyosin A rabbit serum

TABLE 1
SPECIFIC PRECIPITATES OF RABBIT TROPOMYOSIN B WITH ANTI-RABBIT TROPOMYOSIN B

Serum dilutions	1/1	1/2	1/4	1/8
Micrograms of antigen nitrogen added				
160	25.3	69.4	66.2	31.5
40	19.5	80.4*	48.2	18.4
8		62.5*		19.3

Figures in the body of the table represent micrograms of nitrogen precipitated when the quantities of antigen indicated are added to 1 cc. of serum.

quantities of precipitates formed with 2 of the 4 sera. Due to the complexity of the anti myosin antibodies, the degree of crossover was not estimated.

Section 4. Some experiments with sera of rabbits immunized with rabbit muscle proteins. Rabbits were immunized intravenously, without the use of adjuvants, with tropomyosin B and myosin prepared from rabbit muscle and also with tropomyosin A prepared from rabbit myosin. Qualitative precipitin reactions by the dilution method indicated the presence of antibodies in these sera capable of reacting with these muscle proteins. These preliminary tests also showed that some reactions occurred only at room temperature and not in the cold and that diluted sera sometimes gave larger precipitates than undiluted sera.

Reaction of rabbit tropomyosin B with anti-rabbit tropomyosin B rabbit serum. Serial two-fold dilutions of the serum were tested with 8, 40, and 160 μg. of antigen nitrogen. These quantities were added to 1 cc. of the serum dilutions. After three days' incubation at room temperature, nitrogen determinations were carried out on the washed precipitates. The results are shown in Table 1. Assuming that all of the antigen nitrogen is precipitated at the points marked with asterisks, the antibody concentration of the serum may be estimated as about 90 μg. of antibody nitrogen per cubic centimeter. In view of the short incubation and the limitations of the foregoing assumption, this is a minimum estimate. If valid, it would indicate that 2 antibody molecules react with 1 tropomyosin B molecule at equivalence.

Reaction of rabbit tropomyosin A with anti-rabbit tropomyosin A rabbit serum. The experiment was carried out in the preceding manner, except that incubation was continued for six days at room temperature and quantities of antigen nitrogen added to 1 cc. of serum dilution were as noted in the upper portion of Table 2. From the point marked with the single asterisk, 342 μg. of antibody nitrogen per cubic centimeter of serum may be calculated. It also appears that, here, 1 tropomyosin A molecule reacts with 1 antibody molecule.

Reaction of rabbit tropomyosin A with anti-rabbit myosin rabbit serum. In view of the difficulties encountered with the system of cat myosin and anti-cat myosin sera, only qualitative tests were carried out with rabbit myosin and anti-rabbit myosin serum. The antibody titer of the serum was estimated from its reaction with rabbit tropomyosin A. The data are shown in the lower section of Table 2. From the point marked with double asterisks, it may be calculated that the serum contains 325 μg. of antibody nitrogen. These antibodies are directed against rabbit tropomyosin A, the only portion of the antibodies so far estimated. It would seem that 5 antibody molecules react with 1 tropomyosin A molecule at this point, which may indicate antibody excess and consequently, in reality, a higher titer.

TABLE 2
SPECIFIC PRECIPITATES OF RABBIT TROPOMYOSIN A WITH ANTI-RABBIT TROPOMYOSIN A AND WITH ANTI-RABBIT MYOSIN

Serum dilutions	1/1	1/2	1/4	1/8
Micrograms of antigen nitrogen added				
	Anti-rabbit tropomyosin A			
100	150	114	57	52
25	62	(15)	110*	29
6.25	8	7	18	24
	Anti-rabbit myosin			
100	294	102	58	39
25	90	114	61	29
6.25	80	120	88**	29

Figures in the body of the table represent micrograms of nitrogen precipitated when the quantities of antigen indicated are added to 1 cc. of serum dilution.

DISCUSSION

Certain physicochemical properties peculiar to muscle proteins warrant consideration of some technical points with regard to the methods used in this study. Because of the

heat sensitivity of the muscle proteins, the usual incubation at 37° C. before incubation in the cold was omitted and the test was carried out in most cases entirely in the cold. In view of the solubility properties of the proteins studied, a higher than usual salt concentration had to be employed. Both factors tend to prevent precipitation of antigen-antibody complexes. Indeed, the reactions were slow and sluggish compared to other immunologic systems. Only with the system anti-clam tropomyosin A and clam tropomyosin A was an immediate reaction visible, but precipitation was still only partial after three days and did not become complete until the fifth day. Extending the time of the cold incubation seemed inadvisable because of the increased danger of contaminations and nonspecific precipitates observed in control tubes in some prolonged experiments. One week's incubation as a rule seemed to be a fair compromise, with the reservation that the precipitates determined may be only minimum estimates.

With respect to the nitrogen determinations, direct nesslerization always gave results in close agreement with other methods of protein determination under our conditions. The various steps of the experiment—precipitin reaction, washing of the precipitates, digestion with sulfuric acid, color development, and spectrophotometric reading—could all be carried out in the same calibrated tubes without transfer of material. This reduces the size of the sample required and minimizes experimental error. The lower limit of precipitates that can be determined this way is dependent upon the observed blanks, which were regularly 2.5 μg. of protein nitrogen. It was calculated that this amount would be obtained from a monolayer of protein adsorbed on the lower portion of the tube used.

The results presented are in general agreement with earlier findings with regard to the structure of myosin.[1,2] Close similarity of amino acid composition between tropomyosin A and part of the myosin molecule[14] as well as other evidence[15,16] showed that tropomyosin was a subunit of myosin. The cross reactions reported here are consistent with this hypothesis and fail to reveal differences in detail or configuration that would be conceivable despite the identical amino acid composition. With regard to isoantigenicity of muscle proteins, it must be emphasized that the original observation of Kesztyus, Nikodemusz, and Szilagyi[1] on the isoantigenic nature of actin was made at a time when the best available preparation was only about 50% pure. Our more recent experiments[2] were carried out with actin purified by Mommaerts' procedure.[11] According to new data received in a personal communication from Dr. Laki, even this actin may contain as much as 20% tropomyosin. The present experiments showing tropomyosin to be isoantigenic indicate that the antigenic nature of actin proper ought to be reinvestigated at a time when tropomyosin-free preparations of this protein become available in native form. Isoantigenicity of both tropomyosin B and the closely related tropomyosin A, which was demonstrated in this study, may account for the fact that myosin itself, built from these subunits, serves as an antigen in the same species from which it was derived.

The question is sometimes raised whether preparative steps may not so alter these proteins from a given species that they behave as foreign proteins when injected into other animals of the same species. However, the crystalline nature of some of the muscle proteins can be taken as a sign that these proteins are not denatured in the chemical sense. Also, the enzymatic activity of myosin and its ability to contract in the presence of actin and adenosine triphosphate seem to argue against material alterations in the course of the preparation. Furthermore, the globulin fraction of antisera to this protein, labeled with fluorescein marker, stained specifically muscle sections prepared by a variety of procedures.[12,13] It seems unlikely that such different manipulations as extraction with 0.5 M potassium chloride on the one hand and frozen sectioning, glycerol extraction, formol fixation, and so forth on the other should all result in the same type of artifact, indistinguishable by sensitive immunologic reactions. It seems more probable that the intracellular location of these proteins and their fixed position in the structure of the myofibrils prevent their acting as antigens within the animal under ordinary conditions. Thus, identical configuration of structure proteins, without the loss of selective advantage, can be preserved in various species.

In line with this assumption would be the extensive cross reaction between the clam tropomyosin A and the rabbit myosin.

Pathologic processes based on hypersensitivity due to autoimmunization are becoming increasingly recognized, and the possibility of an allergic nature of certain types of muscle diseases has been pointed out by Walton and Adams.[17] The observation that the macrophages surrounding the injured muscle fiber occasionally contain material that stains specifically with the fluorescent antimyosin antibody[3,12] could thus represent a way of transfer of antigenic substance into the reticuloendothelial elements leading to eventual autoimmunization. It is felt that further experiments by immunochemical technics are needed to substantiate this working hypothesis and clarify the nature of the hypersensitivity mechanisms, as well as to establish their role in the chain of events constituting muscle disease.

SUMMARY

1. Myosin, tropomyosin A, and tropomyosin B, 3 structure proteins of muscle, were studied. Ouchterlony plates were used for testing the hemogeneity of the preparations, and quantitative precipitin reactions yielded information on the titer of the sera and the stoichiometry of the reaction.

2. Tropomyosin A prepared from clam muscle appears to be a single antigen. Rabbit sera contained up to 492 μg. N of anti-clam tropomyosin A and antibodies localized in the gamma globulin fraction. At equivalence, 2 antibody molecules react with 1 tropomyosin A molecule, while, in the antibody excess region, 1 tropomyosin A molecule is capable of reacting with 4 antibody molecules.

3. Myosin prepared from cat muscle appeared to be homogeneous in the ultracentrifuge. In the agar diffusion experiments, however, multiple lines were observed when cat myosin reacted with anti-cat myosin rabbit sera.

4. Anti-clam tropomyosin A rabbit sera precipitated cat myosin before but not after these sera were allowed to react with clam tropomyosin A. The supernatants of the mixtures of anti-clam tropomyosin A sera and cat myosin showed a reduced ability to react with clam tropomyosin A. From this, the degree of crossover may be estimated at more than 50%. Similarly, anti-cat myosin sera precipitated clam tropomyosin A, but, due to the complexity of the anti-cat myosin antibodies, the degree of crossover could not be estimated.

5. Rabbits could be immunized with tropomyosin A, tropomyosin B, and myosin prepared from rabbit muscle. Significant titers were observed in the sera. Tropomyosin A prepared from rabbit myosin was precipitated by the anti-rabbit myosin sera, and this reaction could be utilized to assess the titer of the antimyosin sera.

6. The results are discussed in terms of the subunit structure of myosin.

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Vestibular disturbances in epilepsy

Bernard H. Smith, M.D.

THE LABYRINTH diminishes in importance as we ascend the phylogenetic scale.[1] In health, it functions unobtrusively, and we become fully conscious of it only when it is out of order. It probably plays its major role through brain stem reflexes, and much work has been done on the brain stem connections concerned.

There is uncertainty as to the cortical representation of vestibular function, both as to its site and its nature. This study was undertaken in an attempt to elucidate these problems.

Contributing to the uncertainty is the doubt concerning the functions of the various parts of the labyrinth itself.[1,2] The nonacoustic labyrinth is thought to have 2 main functions: kinetic, dealing with changes in the rate of movement, and static, dealing with the position of the head in relation to gravity.

The semicircular canals have kinetic functions only and register angular acceleration or, more simply, changes in the rate of rotation of the body. The macula of the utricle has probably both kinetic and static functions, with sensitivity to both linear and angular accelerations, as well as to tilting of the head. The function of the saccule is less certain. The morphologic similarity between the maculae of the saccule and utricle suggests that the saccule has functions similar to those of the utricle. However, the consensus appears to be against this, and to the saccule is attributed the registration of low frequency vibrations. In support of this is the fact that the saccule has a closer developmental connection with the cochlea than with the nonacoustic labyrinth.

Experimental evidence shows that cortical representation of vestibular functions exists. Spiegel[3] found that in cats and dogs, when the temporal convolutions were sensitized with strychnine, stimulation of the labyrinth by rotation or the caloric method produced convulsive movements. He interpreted this as due to the spread of vestibulotemporal excitation to the motor cortex. These movements failed to appear after section of the eighth nerve.[4] Spiegel also showed that action potentials, led off from the strychninized temporal lobe, increased when the vestibular nerve was stimulated. Walzl and Mountcastle[5] found that evoked potentials from the stimulation of the labyrinth could be recorded in the cerebral cortex between the auditory, rolandic somatic sensory, and second somatic sensory areas. Kempinsky[6] showed that the cortical projection area from electrical stimulation of the vestibular nerve in the cat overlapped the somatosensory area for the face and arms anteriorly and the auditory area posteriorly.

In man, the site of the vestibular cortex has been variously placed. Oppenheim[7] gave a frontal and possibly central cortical localization. Foerster[8] placed it in the superior lip of the interparietal sulcus. Penfield and Kristiansen[9] gave a localization in the posterior-superior portions of the temporal lobe and in the temporoparietal border regions.

It might be deduced from the known or putative functions of the labyrinth that the cortex subserves the following vestibular functions: recognition of the position of the head in space, angular and linear accelerations, and sensibility to low frequency vibrations. It might also be speculated, in view of the brain stem connections, that the vestibular cortex has close connections with the cortical areas subserving vision and eye movements, somatic sensibility, hearing, and visceral and autonomic functions.

To the clinical neurologist, the weapon that lies at hand for investigating the vestibular functions of the cortex is the time-honored

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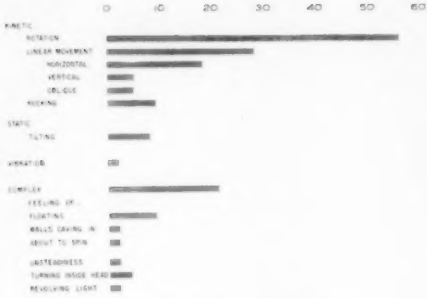


Graph 1. Vertiginous disturbances in 120 patients

study of epilepsy. The electroencephalogram will yield valuable supplementary information, but the present study deals with the clinical aspects.

The approach has been twofold. First, patients have been persuaded to describe, as accurately as possible, the nature of any symptoms that appeared to involve vestibular functions. This was presumed to give a clue as to what vestibular functions are represented at the cortical level. Secondly, disturbances of other bodily functions which accompanied the vertigo were noted. It seemed likely that these associated disturbances would have a cortical representation in the proximity of the vestibular cortex, and, if the site of these other functions were known, the site of the vestibular cortex could, fairly reasonably, be extrapolated.

An immediate difficulty facing the clinician involves nomenclature. There is no single word that covers all aspects of labyrinthine dysfunction. In the past, that portion of vestibular function involving rotation has been segregated and stressed to the neglect of other aspects. "Vertigo," with its etymologic sense of turning, has been accepted as evidence of disturbance of the labyrinth or its connections, whereas other vestibular complaints not involving turning and which patients tend to subsume under the more comprehensive term "giddiness" have been neglected because giddiness is sometimes loosely used to cover other symptoms unrelated to the labyrinth. In brief, giddiness is too comprehensive. A word is needed which is at once comprehensive and exclusive for the symptoms of vestibular disturbance. In this paper, the term "vertigo" has been so appointed.

In the discussion that follows, the distinction between so-called subjective and objective vertigo has not been stressed because it appears to depend on such extraneous factors as whether the eyes are open or closed and to involve interpretation and judgment, as is exemplified by common experience. Thus, a person sitting in a train alongside another train may have momentary difficulty in deciding which train has moved off.

This study involves 120 patients who were considered to have symptoms of vestibular disturbance in their epilepsy. Graph 1 shows the type of disturbance noted. The commonest symptom is a sense of spinning. Besides its actual frequency, it may figure so largely because of its dramatic quality and ease of description. The vertigo is in various planes. The commonest is rotation around the vertical axis; rotation around the sagittal axis is also noted. An example of rotation around the coronal axis, such as might be described as somersaulting, was not obtained, although one patient did describe his sensation as similar to being on a swing. In describing rotation of environment, some described the ceiling as whirling, others the floor, and some the furniture. Actual rotation of the body to the right was described by one patient.

Horizontal movements refer to both side-to-side and fore-and-aft movements. A patient felt he was being pushed to the left; another, that he was being drawn backwards; another, that he was veering to the left; and others, that they were falling backward or to the side. The approach and recession of objects was also described, although this may have explanations other than vestibular dysfunction.

Patients listed as showing vertical movements described their experience in such terms as "going up or down in a fast elevator," "falling into a bottomless pit," "soaring up like a bird," and "hurtling through space." A patient described the ground as coming up to meet him. The rocking movements covered symptoms described as like being in a ship or canoe.

The above disturbances can probably be related to the so-called kinetic labyrinth. The 8 patients listed as showing "static disturb-

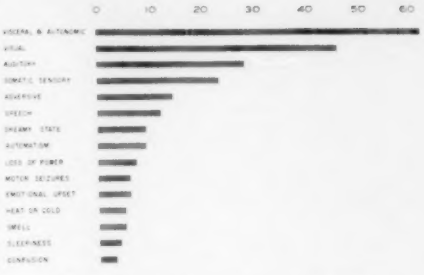
ances" described themselves or their environment as being tilted clockwise, counterclockwise, or in an anterior-posterior plane, the last by 1 patient who felt that the front of the classroom was tilted down and the back of the room elevated.

The above sensations might all be described as primary simple vestibular disturbances. A number of instances were encountered of what might be called primary compound sensations, such as the feeling of movement from side to side combined with rotation or the even more complex feeling of rotation, side-to-side movement, and falling.

The 2 cases listed as possibly showing vibratory disturbance attributable to the saccule described the earth as shaking and the inside of the body as shaking, respectively.

I have dealt with the relatively crude disturbances of vestibular function. A number of patients described experiences that appeared to involve complex vestibular dysfunction at a higher level of integration. A relatively simple example of the more complex disturbance is the feeling that hallucinatory lights are whirling before the eyes. Another patient complained of seeing the door tilted and in quadruple. It has already been mentioned that the psychical disturbance of micropsia associated with recession of objects and the converse phenomenon of macropsia with approach of objects may involve vestibular dysfunction, although they are susceptible of other interpretations.

Several patients had the feeling that the walls were closing in. This disturbance of extrapersonal space may have as its converse certain disturbances of the body image which are sometimes associated with vertigo, namely, a feeling that the body or part of it is changing its size or weight. Schilder[10] and likewise Hécaen and de Ajuriaguerra[11] have stressed the role of the vestibular apparatus in body image formation and distortion. Schilder also pointed out the close relationship of the vestibular apparatus to depersonalization and time appreciation. A patient described himself as floating and as being far away; another described a feeling of unreality and others, that they appeared to be in a dream. In one patient, the vertigo was associated with the illusion that objects were in slow motion. It



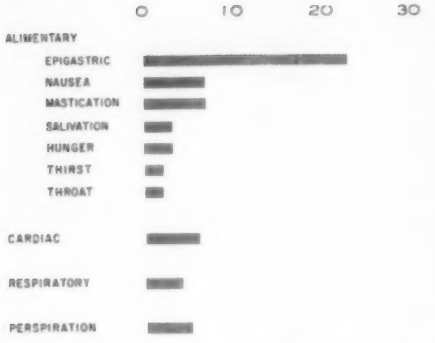
Graph 2. Disturbances associated with vertigo in 120 patients

seems likely that the sense of lightness, implicit in the symptom of floating, is a disturbance of vestibular function at a high level of integration. A patient described his head as feeling heavy in association with the vertigo; others described the head as feeling light. Another patient described his body as floating in some attacks and as spinning in other attacks.

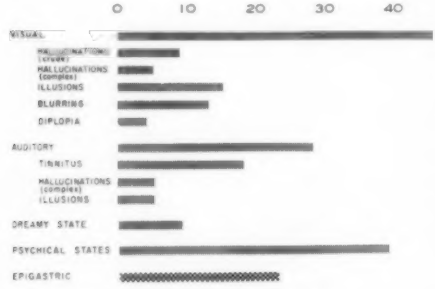
Little understood but of great theoretic interest is the description by several patients that they felt they were about to spin; they claimed there was no actual spinning but the feeling distressed them as much as if they were spinning.

It is difficult to be sure that those patients who felt there was something turning inside their heads had, in fact, vertigo in the sense used here. Perhaps a comparable objective phenomenon was the feeling sometimes described that specific objects in the environment were whirling rather than the environment as a whole.

Graph 2 shows other disturbances associated with vertigo in the epileptic attacks. The preponderance of visceral and autonomic disturbances is perhaps not surprising when it is remembered how frequently such disturbances accompany labyrinthine disorder at a lower level. It will be noted that associated visual disturbances outnumber associated auditory disturbances, which again is perhaps not surprising in view of the close functional relationships between vision and the statokinetic labyrinth. The fairly high correlation with somatosensory and somatomotor disturbances recalls Jackson's[12,13] dictum that vertigo is a sensation of a motor process.



Graph 3. Visceral and autonomic disturbances



Graph 4. Associated disturbances

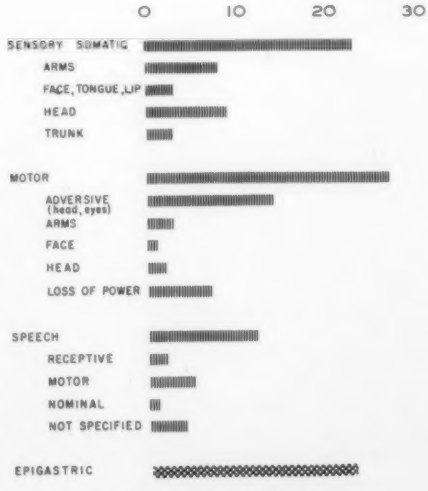
Graph 3 breaks down the visceral and autonomic disturbances; it is seen that by far the commonest correlation is with an epigastric sensation, the anatomic substrate of which is thought by Penfield and Jasper[14] to be in the insula. The nausea and salivation that accompany other forms of vestibular disturbance, such as seasickness, are also seen in the vertiginous form of epilepsy.

Graph 4 shows that crude visual hallucinations are less common than crude auditory hallucinations. This suggests that the primary auditory cortex is in closer proximity or, at any rate, closer functional relationship with the vestibular cortex than is the primary visual cortex. However, the visuopsychic disturbances, more especially illusions of vision, outnumber the auditopsychic disturbances. When the psychic disturbances of vision and hearing are grouped with other psychic disturbances, such as the dreamy state, and more especially if the dysphasias are added, it will be seen that they outnumber the epigastric sensations, crude disturbances of vision and hearing, and motor and sensory somatic disturbances.

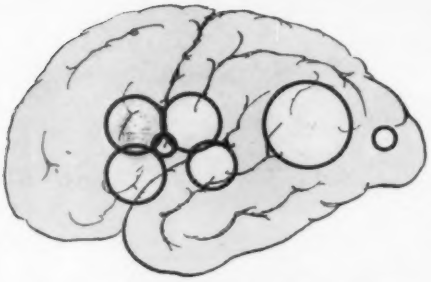
Graph 5 shows that the associated somatic sensory disturbances involve chiefly the head, arms, face, lips, and tongue. The most common motor disturbances are adversive movements of the head and eyes. The phenomenon listed as loss of power is of interest; 7 patients described a curious inability to move their body or their head and eyes or to speak. They described themselves as conscious at these times, and their difficulty appeared to resemble what has been called sleep-paralysis. The importance of the labyrinth and vestibular nuclei in the control of muscle tonus is well known, and it may be that this offers a clue to the cause of the apparent paralysis that seizes these patients.

DISCUSSION AND CONCLUSIONS

Examples have been quoted to demonstrate the diversity of the vestibular patterns that may be released by the epileptic process, presumably at the cortical level. It appears that all the known functions of the statokinetic



Graph 5. Associated disturbances



Summary of the frequency of associated phenomena and possible anatomic substrates

labyrinth are represented at the cortical level. If there is a topographic localization for these various functions within the vestibular cortex, it could not be deduced in the present study.

It appears that the vestibular system has the same associations at the cortical level as in the brain stem and, as is exemplified in such diseases of the peripheral organ as Ménière's disease, connections with the autonomic, visceral, and auditory systems, the eye nuclei, and the motor pathways.

It seems likely that there are various levels of vestibular function in the cortex: a relatively crude or primary level and a complex secondary or psychic level. The symptoms of dysfunction of the primary level are probably closely similar to those of the end organ itself. They may be differentiated from those of the end organ by the fact that epileptic vertigo is frequently associated with epigastric sensations, sensory disturbances, dreamy states, and loss of consciousness.

To translate these functional levels into terms of cortical areas is a hazardous undertaking. The variety of disturbances associated with epileptic vertigo suggests that the vestibular cortex may be extensive or, at any rate, have extensive connections. It seems likely that the cortex subserving primary vestibular functions adjoins the insula, the sensory-motor areas for the face, arms, and head, and, perhaps, the auditory areas. The illustration at left attempts to summarize graphically the frequency of associated phenomena and their possible anatomic substrates. The vestibulopsychic area, if it be localized, may have its epicenter in the region of the angular gyrus. The large circle in the region of the junction of the occipital, parietal, and temporal lobes stresses this role of the vestibule in psychic functions.

The phylogenetically ancient and vital organ of balance, analogously perhaps to the sense of smell, has suffered debasement in the more evolved animals but continues to affect profoundly the higher functions of the brain.

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Metachromatic form of diffuse cerebral sclerosis

III. Significance of sulfatide and other lipid abnormalities in white matter and kidney

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EARLIER PAPERS in this series have described urine sediment findings[1] and metachromatic lipiduria[2] in the metachromatic form of diffuse sclerosis, or metachromatic leukoencephalopathy. For brevity, the second term is used here, abbreviated ML. A previously undescribed increase in cerebroside sulfuric acid esters (CSAE) has been noted in both ML brain and kidney.[3]

Purposes of this report are to [1] document a number of chemical changes in 4 cases of ML and [2] note the meaning of these bare data in terms of pathogenesis when possible, citing from pertinent experiments and recent literature.

The scope of cerebroside sulfuric acid esters is extended beyond this model disease by 2 significant considerations. First, the strong metachromatic staining of normal myelin comes in part from this general type of sulfatide.[4] Of further interest is the cation binding by CSAE and its possible relation to cation shifts involved in the normal nerve impulse.[1-4,70]

MATERIALS

ML in 4 children from separate families was studied in 3 brains and 3 kidneys.* Clinical and pathologic findings, noted elsewhere or to be reported separately, are in all respects typical of well described, classic forms of this disorder.[1-3,69] Control material includes 7 normal brains, 7 normal kidneys, and 6 minimally abnormal brains. Criteria for normality or abnormality in controls include clinical, gross pathologic, and microscopic findings, using toluidine blue and Sudan black B in frozen sections and hematoxylin and eosin in paraffin sections, at a minimum. Cerebral white matter from centrum semiovale was carefully dissected free of ependyma and gray matter; kidneys were stripped of capsule and hilar fat. Controls were of representative and comparable ages, with preference given to younger ages after myelinization. Cases were matched according to location of white matter sample and, insofar as possible, to length of formalin fixation. Fluff from frozen kidneys was used[2] in series I and reextracted with 10 cc. of chloroform-methanol 2:1 per gram of kidney (Fig. 1). Injections of white matter and kidney sulfatides from all ML cases (and controls and CSAE standards) were made in the corpus callosum of weanling and adult Sprague-Dawley male rats, controlled with 30 other pertinent molecules, and studied in stained and unstained frozen sections.[41]

METHODS

Diced tissues were homogenized in a Waring blender at 9° C. for three minutes and dialyzed thirty-six hours against running tap water at 9° C. and against distilled water at 4° C. for twenty-four hours. Lyophilized, powdered homogenates were further dried to constant weight in vacuo over fresh P_2O_5. Lipids were

*W.T., University of Oregon Medical School Hospital No. 232976; D.C., Western Reserve University Hospital No. 10065; W.B., Massachusetts General Hospital No. 19345; R.F., Baylor University Hospital No. F 55-235 (last 2 are isolated cases).

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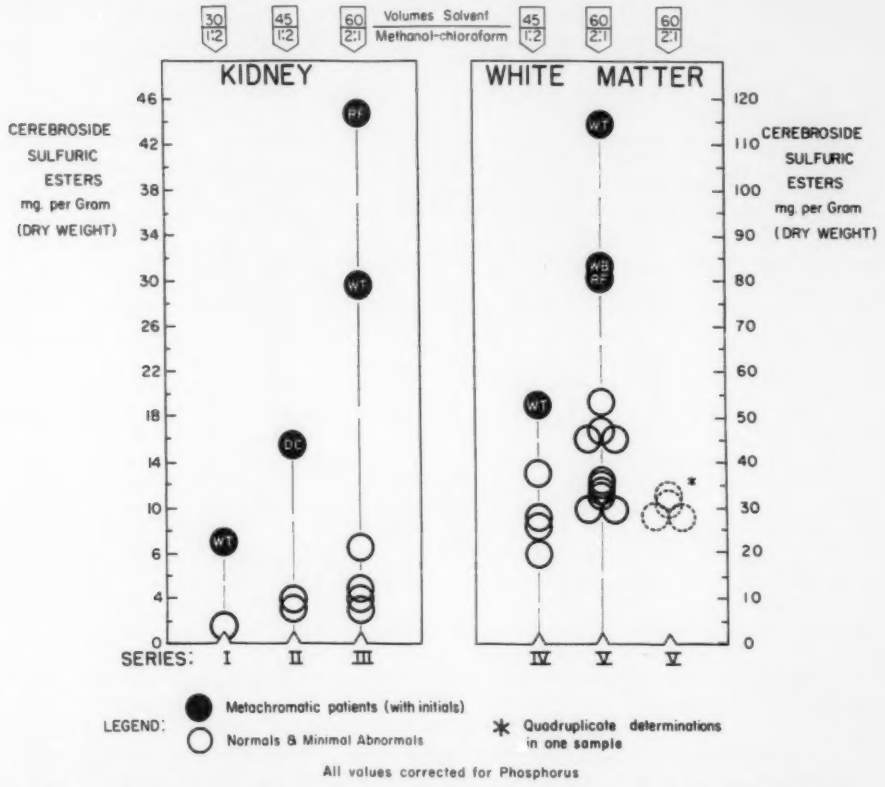

Fig. 1. CSAE values in 5 series. Note consistently higher values in ML despite different technics and extraction mixtures.

extracted from 0.5 to 2 gm. of dry powder with large total volumes of chloroform-methanol in 3 stages (Fig. 1). This and all subsequent procedures were done with a standardized technic throughout each series. Extracts were stirred for twenty seconds at room temperature and promptly capped to avoid evaporation. Prompt centrifugation (Serval, 9,900 rpm, 12,100 G; thirty minutes) at 4° C. separated extractable lipids from residue. Sharkskin paper filtration[2] gave clear lipid extracts. Equilibrated and restored to chloroform-methanol, 2:1, these extracts were freed of water-soluble materials by 0.2 volumes of aqueous NaCl wash (730 mg. per cent)[5] and careful suctioning. Red-pink metachromatic lipids were traced by spot test[2] through all separations.

Partitionable sulfatide fractions were separated, with duplication of the KCl step, in a standardized modification of the procedure of Lees.[4,6,73] Funnels had Teflon stopcocks. Sulfatide fractions were dried to constant weight over P_2O_5 in vacuo. With this procedure, yields from equal volume aliquots of normal white matter have agreed within $\pm 3.8\%$ ($n = 6$). Sulfuric acid ester (SAE) absorptions in dry fractions were read by densitometer at their peak at 8.02 μ. with KBr disk technic on a Perkin-Elmer infrared spectrophotometer M-112.[4,7] For uniformity here, means of 6 SAE absorptions were corrected

by comparison with, and all expressed in terms of, reference samples of 1 CSAE standard, lot B-7,[34] designated CSAE(T), kindly donated by Dr. S. J. Thannhauser. Subtracted from SAE absorption was the absorption at 8.02 μ. of phosphorus-containing compounds in amounts appropriate for % P. Use of phosphoserine or phosphoethanolamine here (with equal molar extinction correction for P, 0.37 × that of S in CSAE) is consistent with the finding of chiefly serine (and ethanolamine) on hydrolysis only.[7,44] Between the P × 2.58 and absorption methods of subtracting for P, provision is thus made for different P-containing compounds.[4] This further increases spreads between ML and controls and to a lesser degree than grossly subtracting P × 25. For other lipids, standard methods were used after reproducible results were obtained (see table).

All colorimetric readings were made in duplicate on a Bausch and Lomb Spectronic 20. Aqueous-methanol and washed, pooled "other lipid" fractions were stored at 4° C. after separation of CSAE fractions. Single phases were made with methanol. Volume aliquots were dried with N_2. All determinations are related back to 1 gm. of original tissue (dry weight) and outliers rechecked. Parallel results were obtained with 2 cholesterol methods. Standard curves and recoveries of cholesterol in ethanol and of its palmitate ester in 1:3 ether-ethanol correspond on a molar basis. Hexosamine was determined as glucosamine.[64] Hydrolysis times in Teflon-sealed tubes were eight hours at 100° C. with 2 cc. of 2 N HCl[59] for dry lipid fractions from 100 mg. tissue and one hour at 100° C. with 1.5 cc. of 3 N HCl for dry aqueous methanol fractions from 100 mg. tissue. AG 50-X8, 200-400 mesh resin was used for separation. HCL was analytical grade (Baker). Recovery of standards was 98.7% ± 4.4%. Gross estimation of %S in representative other lipid fractions was made for purposes of approximation only, using dried residues of volume aliquots equivalent to 250 mg. of tissue in series I, II, and IV and equivalent to 145 mg. in III and V. Corrections were made for mineral ash calculated as KCL. "Phospholipids" equal P × 25. Whatman No. 1 paper was used for chiefly ascending chromatography. Galactose was identified descending at 23 cm., using, separately, s-collidine and 2,6-lutidine. The spot corresponding to the standard sphingosine at a chromatographic migration ratio of approximately 0.8 was found with the chloroform-soluble, water-washed base after hydrolysis in 10% H_2SO_4 in methanol and removal of fatty acid methyl esters. Separation of CSAE fractions into metachromatic, nonmigrating and 2 elongated, metachromatic, migrating, overlapping subfractions (ascending and descending, with average migration ratio values essentially the same as standards, approximately 0.20 to 0.30 and 0.30 to 0.40) was done on Whatman No. 1 or 3 papers or S. & S. 2043b, using the system of Jatzkewitz:[14] isoamyl-butanol-H_2O (108 : 10 : 40). In some cases, the system was varied or replaced with ethanol, n-propanol, ethyl acetate, or buffered H_2O. Staining was done with toluidine blue[2] or rhodamine B. Micropolarimetric optical rotations, kindly performed and interpreted by Dr. C. E. Ballou, were done on 1 to 2 mg. of CSAE in 1 cc. of 2:1 chloroform-methanol. Farrand recording spectrophotofluorometer scans were made with 1 mg. of CSAE per 10 cc. of chloroform-methanol. First melting points are means of 4 direct readings on an Eimer and Amend block apparatus.

Many other lipid analyses, in common with data here, are to be regarded more as first-order approximations, of greater value for comparison within a large controlled series than as absolute numbers. Particularly in lipid analyses, it is clear that significant conclusions require significant numbers of both normal and selected abnormal samples. Values here are to be compared within each series because of technical improvements in methodology from series I through V over three years and use of different samples.

RESULTS AND SIGNIFICANCE

CSAE increase in white matter. CSAE elevations in ML white matter differ statistically from controls.[35] In series V (Fig. 1), highest and lowest sulfatide values in ML are 152 to 214% those of the top normal value. For contrast, healthy persons from ages 4 to 20 fall in the middle cluster from 45 to 53 mg. per gram. Note that the lowest 4 values for white matter in series IV and the lowest 6 in V happen to come from minimally diseased brains or from extremes of age, 15 months, 17 months, and 70 years.

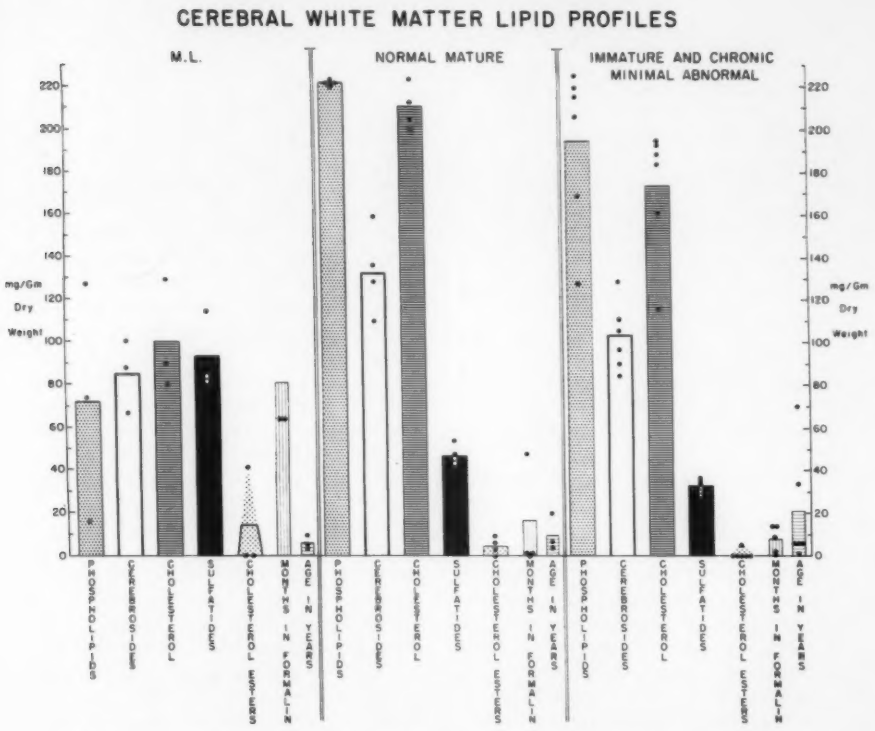

Fig. 2. White matter lipid profiles. Series V. Note reduction of other myelin lipids in all disorders of white matter, especially ML. CSAE elevation in ML is unique. Bars indicate means and dots, separate cases. In ML, highest and lowest CSAE results have p values of $< .05$ and $< .005$ for the entire series, both on uncorrected yields and after correction for SAE and phosphorus.

The increase of CSAE in ML is also *disproportionate* because other myelin lipids are lowered. The histochemical correlate of this is the complete lack of unaffected myelin sheaths in ML "white matter" samples analyzed. These trends are best seen graphically in series V (Fig. 2). Note that, in ML, sulfatides are raised almost as high as mean values for total cholesterol and cerebrosides. Thus, in ML, ratios of CSAE to these other 2 myelin lipids approximate 2:2.1:1.8, respectively (uncorrected). In contrast with ML, even minimal abnormal controls have a low CSAE whenever cholesterol and cerebrosides are low. This parallel fall in CSAE, or lack of normal mature amounts, tends to keep proportions of 1:5.2:3.2, which are more similar to the normal 1:4.4:2.8.

The CSAE excess is of interest in a model disorder like ML because it raises basic concepts of how myelin may become altered in disease. It seems likely that an excess of a normal building block of myelin like CSAE would signify a critical departure, metabolically, from steps leading to the normal myelin complex. Even subtle errors, qualitative or quantitative, affecting CSAE turnover in myelin synthesis or resynthesis might thus lead to a defective and biologically unstable myelin. Given a period of months of disordered equi-

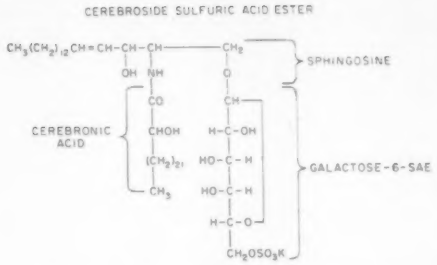

Fig. 3. Structural formula of the CSAE prototype (after Thannhauser[24])

librium, myelin breakdown might occur, even though turnover of CSAE, once formed in whole brain, may well be slow normally.[21]

But the role of CSAE in ML need not be solely a more passive, metabolic one. Note that, structurally, sulfatides have interesting potentialities. In a CSAE molecule, there are units with both lipid and nonlipid solubility properties (Fig. 3). Anionic SAE groups may be considered to confer a strong negative charge, attracting and reorienting cations (+), H_2O, and other positively charged groups.[50] Polar CSAE macromolecules, as structural parts of living membrane systems, might actively participate in physicochemical membrane phenomena. Orderly formation of the many series of micromembrane systems essential to construct the intricately laminated membranes of myelin itself[54,55,68] might thus be deranged in ML.[74] These same potent properties might also render excess CSAE capable of secondarily interfering with enzyme and other chemical reaction systems, for example, those of other myelin precursors. Of interest in the myelin defect in ML are [1] the fragility of oligodendroglia and their secondary mucoid reactions with mucicarmine staining[20,32] and [2] marked breakdown in structure of bone and abnormal connective tissue in growing animals when another sulfuric ester is present in excess.[3,31] Through these 3 overlapping mechanisms, then—metabolic, physicochemical, and chemical—the excess CSAE found could be evidence correlating with an hypothesis developed by Greenfield.[19,20,22] This presupposes in ML a gradual failure to properly build up and renew normal myelin. An attempt is not made in data herein to separate CSAE of dysmyelinization in ML from that of demyelinization or to give a fixed weight for CSAE molecules.

CSAE accumulation in both white matter and kidney appears, descriptively, to constitute a sulfatide lipidosis, with chemical analogies to other lipid storage disorders.[18,29] In each of these, one naturally occurring family of lipids is preeminent. Mechanisms of altered CSAE turnover in ML are under study. They may be considered here, in simplified form, to include greater production, lesser breakdown, improper construction, and excess binding of CSAE molecules. It need not necessarily be assumed that an identical enzymatic defect is common to all families[41] or that various encephalopathies[66,67] with metachromasia represent CSAE lipidosis as studied here.

CSAE increase in kidney. Greatest contrasts between ML and normal are in kidney. Here, normal CSAE values are low, averaging only 3.3 to 4.6 mg. per gram (II, III). In ML kidneys, in series III, mean elevation is 9 times normal.

ML kidneys keep their relatively normal structure. Marked CSAE increase in kidney is thus a critical point because it minimizes 2 serious sources of error in white matter, leading to an apparent rather than actual increase. One artifactual "increase" is inherent in dry weight calculations when tissue is simply more concentrated by disease.[53] A second might come from extracting more of certain lipids normally bound in tissues out of samples already broken down in structure by disease, for example, ML white matter. Data here do not establish how much excess CSAE comes from intrarenal synthesis and how much reaches tubules from outside sources. Soluble sulfuric acid esters cause metachromasia in tubule cells after experimental systemic injections.[3]

During life, it is not likely that more than minute quantities of kidney CSAE go on to enter a twenty-four-hour urine sample of a non-ML patient. On spot tests, practical diagnostic differences between fluff[2] from controls and ML urines begin, at least, as quantitative ones. CSAE lipiduria is in such an excess in ML cases studied that even small aliquots[2] of fluff are metachromatic. Controls thus far have not had the red-pink color for further aliquot

dilution or grading technics.[2] Calculations in series I suggest that some CSAE escapes with further processing of H_2O-washed fluff into pooled other lipid fractions.

Molecular components of CSAE. The conventional structure for CSAE[33,34,37] has its SAE group on the 6 carbon of galactose (Fig. 3). In this acid ester group, CSAE would differ from cerebrosides such as cerebron (phrenosin), which are likely precursors.[21] From chromatographic spots having the same migration ratio values as galactose and sphingosine, it may be concluded that all ML sulfatide fractions here, like their controls, are galactosphingosulfatides, with no indication of sugars other than hexoses.

CSAE fractions in vitro are strongly metachromatic, doubly refractile, and slightly pink with PAS. The primary mechanism of their metachromasia at an acid *p*H typical of ML under these conditions may be discretely related to the dissociated sulfuric acid ester groups on CSAE macromolecules. Hydrophilic potentialities of acidic groups (such as SAE) may contribute to this metachromasia.[50] Even 0.01 cc. of 10^{-4} molar CSAE is red-pink with toluidine blue on Whatman No. 1 filter paper.[2,3] Not metachromatic are equimolar spot concentrations of CSAE constituents—sphingosine, cerebron, cerebronic acid, galactose, and the sulfuric acid ester of galactose—and spots representative of possibilities in possibly coinciding molecules or groups, for example, sphingomyelin, dimyristoyl phosphoethanolamine and phosphocholine, ATP, and phosphoserine. Polygalactose SAE is metachromatic.

CSAE increases, originally noted in both white matter and kidney in a previous preliminary report from this laboratory,[3] are generally confirmed indirectly in white matter in anthrone determinations for hexose noted by Jervis[71,72] using fractions designated as sulfatide after column separation and in a preliminary chromatographic and spot test report on white matter alone by Jatzkewitz.[14] Valid reservations[14] were placed on attempts to use plus-minus estimates of paper spots to assay them quantitatively with technics used in the inconclusive number of control brains and compounds mentioned. It may be noted further that even a known quantity of CSAE spotted at the application point may have its staining intensity variably depressed when it is admixed with certain other lipids (toluidine blue and rhodamine B).[73] Considered elsewhere[36,47] are possibilities of inconclusive qualitative identification by only chromatographic spots and columns of molecules in heterogeneous extracts with one solvent system and without definite sulfur identification.[72] Methods of separation used, including those in the present ML study, must still be regarded as in process of characterization in disease states.

In ML, metachromatic deposits in gray matter cytoplasm may reflect excess CSAE and/or hexose SAE groups interchanged between CSAE and ganglioside moieties.[23] Because most ganglion cells are so close to myelin around axons nearby, meaningful quantitative analysis of these deposits in ML, as contrasted with controls, is not attempted here. Retinal ganglion cell deposits in ML,[49] lacking nearby myelin, apparently do offer one approach to this situation.

Cerebrosides. Cerebroside precursors of CSAE could be lowered if they were metabolically diverted into an excess of CSAE. Cerebron is also an important constituent in myelin ultrastructure. Such a diversion would itself provide a metabolic mechanism in ML for both defective myelin synthesis and attrition and dissolution of myelin. This mechanism might finally appear in our data by low corrected values for true cerebron-like cerebrosides, lowered proportionately more than those for cholesterol, another myelin lipid. It is of provisional interest that, of 12 white matter ratios thus recalculated, only those in the 3 typical ML cases have this trend. The mixed case (W.B. V), histologically earliest in evolution, falls in with controls (see table). To establish this metabolic mechanism in ML would require separating it from the more nonspecific drop of cerebrosides in any myelin breakdown, with white matter studies early in disease, certain controls demyelinized to exactly the same degree, precise separations, and provisions for different turnover rates in different cell populations. Cerebrosides here, as elsewhere,[18,53,65] are higher than for true cerebron alone because they include some sulfatide galactose. This must be subtracted to have a

SERIES	PATIENT	DIAGNOSIS KIDNEY OR WHITE MATTER	AGE (Death / Onset)	SEX	ORGAN	ABNORMAL M. L. DEPOSITS (HISTOLOGICAL) pH 2	INTERVAL IN 10% FORMALIN M = month Y = year	SULFATIDE FRACTION CSAE mg./gm.	% S	% P	HEXOSE	BASE
I KIDNEY	W T	METACHROMATIC LEUCODYSTROPHY	9 / 5	M	KIDNEY	++	5 M FROZEN - 30 °C	6.9		0.56		
	M N	" NORMAL "	34	M	"	0	1 W FROZEN - 30 °C	1.5		0.70		
II KIDNEY	D C	METACHROMATIC LEUCODYSTROPHY	3 6/12 / 1 7/12	M	KIDNEY	++ - +++	10 Y	15.4		0.75	GALACTOSE	SPHINGOSINE
	D W	" NORMAL "	1 6/12	M	"	0	1 M	3.9		2.56		
	M W	" NORMAL "	8	M	"	0	12 M	2.6		1.80	GALACTOSE	SPHINGOSINE
III KIDNEY	R F	METACHROMATIC LEUCODYSTROPHY	5 / 1 6/12	M	KIDNEY	+++	29 M	44.9	3.27	0.58	GALACTOSE	SPHINGOSINE
	W T	METACHROMATIC LEUCODYSTROPHY	9 / 5	M	"	++	16 M	29.8	2.21 *	0.58	GALACTOSE	SPHINGOSINE
	D S	UNCLASSIFIED LEUCODYSTROPHY	7 / 1 3/12	M	"	0	3 M	6.6		2.77		
	A D	" NORMAL "	2 1/2	F	"	0	9 M	4.7		2.88	GALACTOSE	SPHINGOSINE
	G S	" NORMAL "	3 1/2	F	"	0	11 M	4.1		2.11		
	R M	" NORMAL "	6	M	"	0	14 M	3.0		3.63		
IV WHITE MATTER	W T	METACHROMATIC LEUCODYSTROPHY	9 / 5	M	WHITE MATTER	+++	14 M	52.2	2.32	0.48	GALACTOSE	SPHINGOSINE
	D W	" ? NORMAL " (IMMATURE)	1 5/12	M	"	0	1 M	15.9		1.37		
	W K	" NORMAL " (AGED)	70	M	"	0	6 M	28.1		1.74		
	D S	UNCLASSIFIED LEUCODYSTROPHY	7	M	"	0	1 M	37.3		1.54		
	C V	LEUCODYSTROPHY (MULTIFOCAL, SUDANOPHILIC)	32 / 31 1/2	M	"	0	14 M	27.6		2.38	GALACTOSE	SPHINGOSINE
V WHITE MATTER	W T	METACHROMATIC LEUCODYSTROPHY	9 / 5	M	WHITE MATTER	+++	16 M	114.5		0.44	GALACTOSE	SPHINGOSINE
	R F	" "	5 / 1 6/12	M	"	+++	29 M	81.3	2.71	0.19	GALACTOSE	SPHINGOSINE
	W B	" "	3 7/12 / 1 6/12	F	"	++	16 M	82.1	2.19	0.47	GALACTOSE	SPHINGOSINE
	S W	" NORMAL "	7	F	"	0	12 M	53.5		1.87		
	D M	" NORMAL "	9 6/12	M	"	0	1 M	45.2		1.47		
	R Y	" NORMAL "	4	M	"	0	1 W	45.3		1.67	GALACTOSE	SPHINGOSINE
	R G	" NORMAL "	20	M	"	0	6 W	46.8		1.71		
	W H	UNCLASSIFIED FAMILIAL POLIODYSTROPHY	6 / 5 1/2	M	"	0	9 M	38.4		1.79		
	M M	" NORMAL " (IMMATURE)	1 5/12	M	"	0	1 M	32.5		1.63		
	W K	" NORMAL " (AGED)	70	M	"	0	8 M	39.6 *		1.27		
	L C	CHRONIC 4TH VENTRICULAR OBSTRUCTION ACUTE CEREBRAL EDEMA	6 / 1 7/12	F	"	0	14 M	33.8		2.10		
	S E	FAMILIAL POLIODYSTROPHY	6 / 1	M	"	0	2 M	29.3		1.69		
	B R	CHRONIC MULTIPLE SCLEROSIS	34 / 23	M	"	0	14 M	34.8		1.67		
	METHODS							(6) (7)	(14)	(8)	(23) (30)	(60) (61) (62)
DEVIATION FROM MEAN IN RANDOM DUPLICATES (n = number determinations)								* ± 8% (n = 4)	* 2.34 mb corrected			

gross estimate of residual, nonsulfuric esterified cerebrosides for discussion. Qualified evidence that a residual cerebroside compartment is not only a calculated one are chromatographic spots comparable in average migration ratio values of 0.8 with cerebron standards, distinct from sphingomyelin and cephalin, and as evident in all ML cases as in controls, when quantities appropriate for this figure are used. Evidence of CSAE in other lipid fractions[4] is always much greater in ML cases and includes %S, absorption at 8.02 μ., and metachromatic spots comparable in chromatographic migration ratio with CSAE standards.

SERIES	PATIENT	OTHER LIPID FRACTION: TOTAL CHOLESTEROL mg./gm.	TOTAL CHOLESTEROL mg./gm.	CHOLESTEROL ESTERS mg./gm.	CEREBROSIDES (GLYCOSPHINGOSIDES) = (GALACTOSE x 4.6) mg./gm.	"RESIDUAL CEREBROSIDES" = (CEREBROSIDE GALACTOSE - "S as CSAE" GALACTOSE) x 4.6 mg./gm.	CHOLESTEROL "RESIDUAL CEREBROSIDES" RATIO	% S Units.	"S as CSAE" = (ASH-CORRECTED S x 29.6) mg./gm.	HEXOSAMINES mg./gm. AQUEOUS PHASE	HEXOSAMINES mg./gm. WASHED LIPID	HEXOSAMINES mg./gm. TOTAL	TOTAL PHOSPHOLIPIDS
I	WT	19.3		7.1	12.4	"0" (-13.4)		.46	31.7	0.58	0.63	1.21	24.0
K	NN	21.6		8.6	8.1	7.3		.01	0.9	0.96	0.89	1.75	43.0
II	DC	26.6		10.0	10.0	3.6	7.4	.07	7.1	0.61	0.66	1.49	15.2
K	DW	16.8		10.3	6.5	6.3	2.6	0	0	0.54	0.68	1.32	46.3 *
	MW	17.0		3.6	5.1	5.1	3.3	0	0	0.68	0.60	1.08	27.7
III K	RF	28.9	26.4	6.2	14.2 *	13.9	2.2	.02	0.3	0.68	0.62	1.89	54.2
	WT	30.0	24.2	9.3	11.6	11.6	2.6	0	0	0.44	0.58	1.02	79.4
	DS	22.8		6.7	11.2	11.2	2.0	0	0	0.79	0.92 *	1.71	67.6
	AD	36.1	31.1	15.1	7.8					0.67	0.92	1.59	45.7
	GS	25.6		7.5	14.3					0.66	1.16	1.82	43.3
	RM	28.4		9.9	20.6	20.6	1.3	0	0	0.78	1.05	1.81	35.3
IV W M	WT	116.4		8.3	44.3	19.2	6.1	.19	27.0	1.00	0.89	1.89	168.4
	DW	191.7		44.4	74.0	63.1	3.0	.05	12.0	0.95	0.82	1.77	169.1
	WK	169.2		44.9	103.1	96.4	1.8	.06	8.5	0.61 **	0.36	0.97	195.5
	DS	171.8		32.4	69.6	67.0	2.6	.02	2.9	0.82	0.71	1.53	184.8
	CV	165.5		36.9	116.0	116.0	1.4	0	0	0.87	0.37	1.24	180.2
V W M	WT	139.4	118.6	0	56.9	34.6	3.7	.14	25.5	1.06	1.00	2.05	127.4
	RF	75.9	75.9	0	100.0	21.5	3.7	.36	86.5	0.94	0.93	1.87	15.7
	WB	80.7	84.5	41.4	38.1	37.2	1.0	.12	34.0	0.93	0.98	1.91	74.4
	SW	232.6		9.3	128.7	128.7	1.7	0	0	0.58	0.85	1.43	222.5
	DM	200.3	168.4	0	152.0					0.49	0.80	1.29	223.5
	RY	204.9		2.9	110.0	110.0	1.9	0	0	0.64	0.86	1.50	221.6
	RG	212.2		6.0	136.0 **					0.61	0.61	1.22	230.5
	WH	198.3		0	110.7					0.87	0.72	1.59	218.5
	MM	194.6		0	94.6					1.09	0.84	1.93	224.9
	WK	198.1 * 192.4	173.7 * 175.3	0 * 0	138.5					0.56	0.76	1.32	205.7
	LC	181.2		0	80.0	77.4	2.1	.05	13.8	0.73	0.63	1.36	168.9
	SE	189.4		0	105.4					0.89	0.89	1.77	215.4
	DR	134.4	108.3	5.2	96.7	96.7	1.2	0	0	0.92	0.96	1.84	138.1
METHODS		(11)	(12)	(11)	(10)			(24)		(16) (18)			(8)
DEV. FROM MEAN		* (n = 2)			* ± 5.96 (n = 5) ** ± 4.86 (n = 4)					MINIMUM DEVIATION (mg.): 0.07*, 0.04**, 0.09* (n = 3) MAXIMUM DEVIATION (mg.): 0.35*, 0.39**, 0.30* (n = 3)			* ± 0.96 (n = 6)

Phosphorus in other lipid and CSAE fractions. Some low %P reflects decrease in P in formalin post mortem,[15] but some signifies a marked lack of myelin in ML before death as well. Only in ML kidney are 2 total phospholipid figures in ML above means for the age (III). This may reflect some elevation during life, in view of their longer fixation. Fresh frozen material would clarify this point.

The CSAE fraction obtained in lesser yield from fluff phase in ML was slightly lower in %P from the control (I), and 1 CSAE fraction from fixed ML kidney (W.T. III) as well as 2 from ML white matter (W.T., W.B. V) had

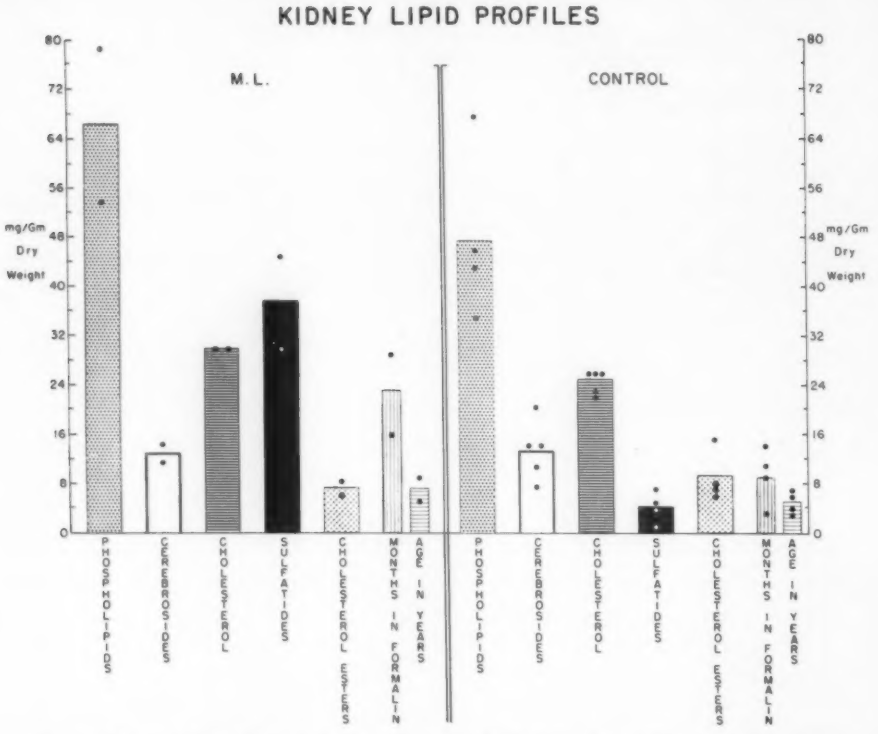

Fig. 4. Kidney lipid profiles. Series III. Average CSAE elevation in series II and III is 4 to 9 times normal ($p < .01$ for entire series on uncorrected CSAE yields and $p < .005$ after corrections). Other lipids maintain approximately normal proportions in contrast with their loss in devastated ML white matter.

considerably less %P than their controls with comparable fixation periods.

The conventional structure for CSAE[33,34,37] contains no phosphorus, but P in sulfatide fractions has long been noted[38] (exception:[39]). Recent chromatographic evidence has pointed to possibilities of extraneous P (for example, on phosphatidyl serine[8,73]) and/or of 2 co-existing subfractions,[6,14] one like this recognized prototype, the other a more mobile phosphated sulfocerebroside. Using several chromatographic systems, 2 metachromatic subfractions do tend to separate with comparable migration ratio values in each of these 6 ML, in each control, and standard CSAE spots applied. The more mobile subfraction is smaller and less dense; both are distinct from standard cephalins and sphingomyelin. Weighed, hydrolyzed, unseparated CSAE fractions yield small spots with migration ratio values in 2 systems[44] consistent with serine and traces of ethanolamine, less evident in all ML cases (which are visibly less yellow). While quantitative assignment of molecular site(s) of all of this P is thus not yet available, one corollary used in corrections is that some of the typically less P of ML fractions may be attached to these molecules. It is inherently preferable to measure cerebroside sulfuric acid esters in terms of their distinctive SAE groups. Other evidence suggests that phosphoric and SAE groups found in normal white matter lipid ex-

tracts are chiefly referable inside formed macromolecules of myelin.[42,52]

Cholesterol esters, cholesterol, and myelin catabolism. Esters of cholesterol increase in usual forms of myelin breakdown.[65] Steps leading to this are not clear. In ML, some loss of preformed "myelin" is consistent with clinical and microscopic findings, particularly in a child like W.T., who developed normally for five years and then regressed.[1] Yet a paradox in ML has been that, while such patients do lack myelin, they also lack sudanophilic phagocytes, which are traditional evidence of previous myelin breakdown. Starting with some defective myelin anabolism (because of a CSAE disorder), however, it would follow that breakdown or dissolution of this myelin would also be proceeding in an abnormal situation. Thus, esterification during this catabolism need not be normal but could also be changed (for example, through factors such as a diversionary decrease in fatty acid availability or altered production and turnover in esters formed, and so on).

Note that cholesterol esters are present in ML only in W.B. (rechecked), the sole child having red-orange perivascular phagocytes with Sudan IV. This case has elements, then, of a mixed metachromatic and sudanophilic case. It shows that a spectrum chemically consistent with the usual myelin breakdown is not incompatible with at least one phase of ML, a point confirmed in part only by the autopsy finding of sudanophilic material in a previous brain biopsy site (through cortex).[63] A trend in ML kidneys toward slightly more free cholesterol than controls the same age (Fig. 4) may reflect nonspecific lipid accumulation similar to other lipidoses.[29,30,46] In ML, this type of added variable limits the comparison of cholesterol cerebroside ratios more with normal kidneys than with the abnormal control brains used.

Lipid hexosamines. Reproducible values for hexosamines are difficult to both obtain and interpret,[16,40] particularly in heterogeneous extracts.[13,65] Edgar[13] noted increased total hexosamines in unwashed dry white matter extracts (chloroform-methanol, 1:3) in some leukodystrophies. This increase is not specific for ML, nor is galactosamine itself metachromatic. Hexosamine trends in white matter here are toward an increase in ML in both aqueous and lipid phases. This contrasts with normal and abnormal children of comparable age. The ML white matter with highest CSAE is highest in hexosamine. Note that data on ML kidneys do not follow this same trend. In this study, hexosamine appears to be less a consistent or essential accompaniment of CSAE per se than of altered white matter. (It cannot be concluded that hexosamine in ML white matter comes from retained blood high in hexosamines, for kidney values would likely be raised too. Serum alpha-2 globulin fractions are high in ML cases cited[1,2,41] and nospecifically increased in other chronic illnesses.) Possibly correlated, microscopically, with such an increase in ML are qualitative changes such as increased astrocyte cell bodies and tough fibrous processes, phagocytes, degenerative products from some axons, oligodendroglia, and fibrous proliferation in vessel walls. Another recent interpretation is that hexosamines are only relatively increased due to their concentration in white matter by disease.[53] It would, however, seem plausible for several mechanisms to coincide.

Histochemical correlates of sulfatides in ML. A test tube excess of a compound need not necessarily be directly concerned with primary stages of a disease. It was crucial to test whether the sulfatides found do account for at least some of the different colors so distinctive of human ML. Sulfatide fractions isolated out of human ML white matter were accordingly injected back into living white matter of the rat. It is relevant to note here briefly that sections made after two to three weeks in vivo already show abundant material in phagocytes. With toluidine blue, colors evolve in these cells through stages morphologically and histochemically similar to those in human ML, for example, first through shades of blue and red and later in certain distant microglial phagocytes toward reddish-golden-brown, only the latter again being doubly refractile[41] (Fig. 5). All, typically, show no sudanophilia with Sudan IV and no dense Sudan black B staining,[43] and are PAS positive. In human ML, reddish metachromasia histochemically gave the most consistent over-all correlation with CSAE yields obtained chemically. Clinically, patient W.T. with latest onset and longest duration

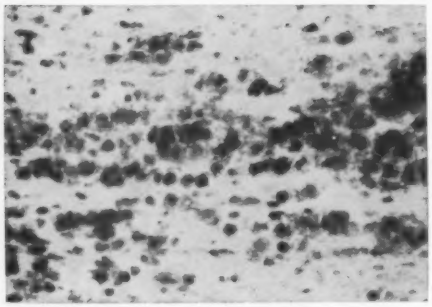

Fig. 5. CSAE in rows of phagocytes in interfascicular spaces. Rat corpus callosum, three weeks after injection. Toluidine blue, *p*H 5. × 120

had most CSAE and microscopic material in white matter.

Polyphenols and catecholamines. Diezel proposed that more brownish metachromasia in ML[1] represents a glycerol-phosphatide-polyphenol combination,[17] subsequently including in the latter a small amount of norepinephrine.[48] Quantities in control diseases are necessary for evaluation. In ML, negative charges on SAE groups do offer the possibility of secondary complexes in vivo with positive-charged amino groups,[2] among them catecholamines in certain nerve cells or from interrupted axons. Precedent for this in ganglion cells is in normal adrenal medulla, in which the normal association of catecholamines with ATP may reflect binding to negatively charged phosphoric acid groups on ATP.[56,57] No positive evidence was noted for catecholamines staying tightly bound to CSAE fractions throughout the mild isolation technic used. Examined were infrared scans (M-112) and excitation and emission peaks from ML brain (W.B.) and kidney (W.T. III) in the sensitive spectrophotofluorimetric method.[28] Certain overactive systems of sulfuric esterification[51] might increase CSAE and/or phenol sulfuric esters. Phenols that are disposed of by sulfuric acid esterification might increase with diversion of SAE groups toward CSAE. Causes for pigments in lipid complexes[43,45] thus need clarification in ML, as do mechanisms of metachromasia and myelin loss experimentally caused by other aromatic hydrocarbons.[58]

Other studies. In further studies, CSAE fractions W.T. and D.M. (V) and W.T. (III) were dissolved in warm chloroform-methanol (1:1, 7 mg. per cubic centimeter). At −30° C., fine white filtered precipitates were present in excess in ML cases, qualitatively identical with CSAE(T) (Fig. 6), and had molar absorptions greater than unprecipitated CSAE(T) or CSAE(R). Dr. N. Radin[27] kindly furnished the latter as the sodium salt, designated CSAE-(R) (melting point 195° C.; molar absorption CSAE(R) = CSAE(T) × 1.35). Considering small sample quantities, differences of significance would be difficult to attribute to optical rotation values among these 5 purified CSAE fractions. (Wave length 340:0.049, .041, .046, .030, .043; wave length 400:0.028, .017, .022, .012, .026, respectively).

Melting points of W.T. and CSAE(T) standard were the same (210° C.); that of D.M. was 207° C. Values for S in 11 mg. of unreprecipitated ML fractions[24] approximate an average of 2.5% which is within ranges noted by others.[34,39]

Routine infrared analysis shows no striking qualitative differences among comparable ML, normal, abnormal, or standard CSAE (Fig. 6) nor do representative double-beam, higher resolution technics (M-21 studies include ML cases W.T., W.B., and R.F. in I, IV, and V). SAE absorption does not change throughout polarization of infrared beams (W.T. I, CSAE-(T), N.N.I., with M-21). This may be an indication of SAE absorption coming from 1 general locus or 1 plane on the molecule.

In view of the formalin-fixed material used in most ML studies, it might be noted that [1] increased CSAE, metachromasia, and S are also found in unfixed ML kidney (I); [2] heavy metachromatic deposits are still seen in ML tissues fixed many years; and [3] formalin has relatively slight effect on cholesterol and cerebrosides, myelin indexes used.[15] Substances soluble in formalin would be unlikely to be directly encountered in this study.

SUMMARY AND CONCLUSIONS

1. Cerebroside sulfuric acid esters (CSAE) and other lipids were measured in controlled series of human white matter and kidney. Statistically significant elevations of CSAE occurred only in metachromatic leukoencepha-

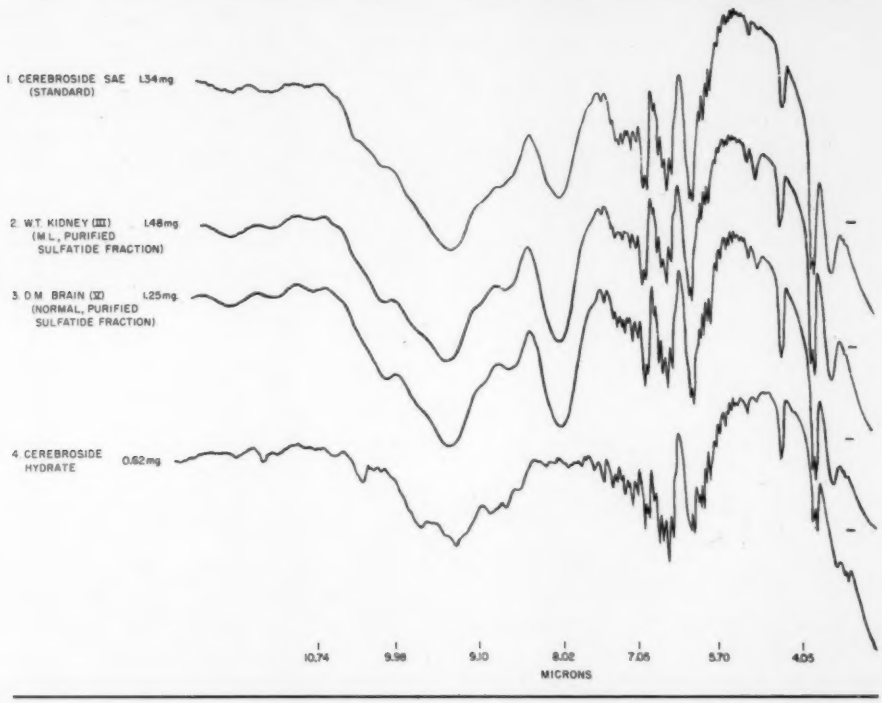

Fig. 6. Infrared scans of purified compounds. Note [1] identity between CSAE(T) standard and those sulfatides from ML kidney and normal brain and [2] strong downward SAE absorption peak at 8.02 μ. (absent in cerebroside hydrate that lacks SAE groups). Lines at right indicate log $\frac{I^{\circ}}{I}$ value of 0.5.

lopathy (ML). Controls with even minimal disorders of myelin had lower than normal CSAE.

2. The CSAE excess is an actual and not only an apparent one, as shown by the even greater increase in kidneys, where structure is relatively preserved.

3. CSAE samples in ML are galactosphingosulfatides, strongly metachromatic, doubly refractile in polarized light, and pink with PAS. Their primary mechanism of metachromasia under conditions cited may be discretely related to dissociated sulfuric acid ester groups on sulfatide macromolecules.

4. In ML white matter, CSAE values are disproportionately elevated, compared to low values for other myelin lipids such as total cholesterol and cerebrosides. Lowering of other lipids correlates histochemically with the lack of myelin. A proportionately greater fall of cerebron-like cerebrosides than of cholesterol is a possibility raised and qualified in ML white matter.

5. Cerebroside sulfuric acid esters are normal constituents of white matter, correlate with some of the intense metachromasia of myelin sheaths, and appear chromatographically in overlapping subfractions. Normal total CSAE values by methods cited were in a range of 45 to 53 mg. per gram.

6. CSAE elevation in ML implies a defect in sulfatide turnover. General causes for such a turnover defect are noted, as are mechanisms by which it and its accompaniments

might in turn interfere with proper synthesis, renewal, and removal of myelin.

7. Quantitative increases of CSAE in both white matter and kidney suggest a working definition of ML biochemically as a sulfatide lipidosis, descriptively resembling the lipid storage diseases. Qualitatively, evidence presented thus far does not consistently separate CSAE in ML from controls.

8. The one elevation of cholesterol esters in ML correlates histologically with phagocytes staining red with Sudan IV. In ML kidney, free cholesterol values slightly above control values may reflect some nonspecific lipid accumulation. Hexosamine increase is greatest in the ML white matter with the highest CSAE. Evidence is lacking for an increase in hexosamine in ML kidney here or for catecholamines in CSAE fractions.

9. CSAE fractions from human ML white matter evolve in phagocytes in rat white matter through stages morphologically and histochemically similar to many of those in their human ML counterparts.

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Subarachnoid hemorrhage in meningiomas of the lateral ventricle

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MENINGIOMAS growing within the lateral ventricle of the brain are rare but clinically interesting tumors that have attracted special attention during the past 2 decades. Since Cushing and Eisenhardt's review[1] of 19 cases of meningioma of the lateral ventricle including 2 of their own, some additional 50 cases have been recorded.[1–11] The value of angiographic study in the diagnosis of meningiomas of the lateral ventricle was discussed by Huang and Araki[9] in 1954. Since our first case,[5] a report of which was included in Cushing and Eisenhardt's series, we have operated on 6 more patients with meningioma of the lateral ventricle.

This paper will describe 2 of these patients who at first were erroneously believed to have ruptured cerebral aneurysms because of the acute onset of their illnesses with severe subarachnoid hemorrhage.

It is well known[12–16] that subarachnoid hemorrhage of the type seen in ruptured intracranial aneurysm does occur in brain tumors. In an analysis of 41 cases of brain tumors presenting clinically as ruptured cerebral aneurysms, Glass and Abbott[14] found that 50% were gliomas, 25% were pituitary tumors, and about 15% were intracranial vascular tumors, which naturally may be expected to bleed sooner or later. To this last group belong papillomas of the choroid plexus.[13,17]

Surprisingly enough, from a review of the available literature, it appears that acute onset with subarachnoid hemorrhage in patients with intraventricular meningioma has not been recorded hitherto. Subarachnoid hemorrhage is probably an uncommon manifestation of these tumors. Nevertheless, we think that its occurrence in 2 of 7 patients with intraventricular meningioma is clinically significant and furnishes an additional argument for carrying out angiographic study in patients with subarachnoid hemorrhage.

Case 1. A 34-year-old woman was admitted to the Neurosurgical Department on April 17, 1954. She had been well until late in the night before admission, when she suddenly had severe headaches and vomited profusely; later, she became disoriented and drowsy. Neck rigidity and extensor plantar reflexes were found. The patient was referred to hospital with the diagnosis of acute cerebrovascular accident.

On admission, the patient was in coma. Strong neck rigidity, facial asymmetry, anisocoria with a dilated left pupil, and ptosis of the left eyelid were noted. A fresh subhyaloid hemorrhage was seen in the left eye; the right ocular disk was flat, with sharp borders. Slight right hemiparesis was found. A positive Babinski sign was obtained on the right side. Blood pressure was 110/80 mm. Hg. On lumbar puncture, the cerebrospinal fluid was grossly hemorrhagic and under increased pressure (300 mm. H_2O). Electroencephalographic examination showed an 8-cps borderline alpha rhythm over the right hemisphere and 3-cps slow waves of high voltage over the posterior temporal and parietal regions of the left hemisphere.

Roentgen films of the skull showed calcifications in the parietotemporal region (Fig. 1), which on frontal views were situated in the depth of the hemisphere.

The sudden onset without any previous symptoms of severe subarachnoid hemorrhage with left oculomotor paresis was suggestive of ruptured aneurysm of the posterior communicating artery. Arteriovenous aneurysm in the parietotemporal region also was considered in view of the calcification seen on straight roentgen films.

However, left carotid angiograms failed to disclose any vascular malformation. Frontal views did not show any contralateral displacement of the anterior cerebral arteries. On lateral views (Fig. 2), there was a noticeable elevation of the middle cerebral arteries, the terminal vessels of which were somewhat stretched. No extravasation or abnormal pooling of contrast material was seen.

From the Neurosurgical Department, Beilinson Medical Center, Petah Tikva, Israel.

The patient remained in coma during the days after arteriographic study. Gradually, her condition improved. The subhyaloid hemorrhage slowly reabsorbed, and she started to respond to stimulation. The ptosis diminished, and, three weeks after admission, she was sufficiently lucid and cooperative for a complete examination. No neurologic disturbances were found on May 25. The ocular fundi were normal, but complete right homonymous hemianopsia was found. Control electroencephalographic examinations showed a steady general improvement of the records, and, already on May 23, only slight left posterior temporal residual abnormality was noted.

On June 15, a control lumbar puncture was made. The cerebrospinal fluid was xanthochromic and under normal pressure. Pandy test was opalescent. There were 3 or 4 cells per cubic millimeter which were lymphocytes and 67 mg. per cent of protein. Mastic curve was 012110.

In mid-July, the condition of the patient changed. At first, she had occasional mild headaches. On July 25, the headaches became severe and she vomited and became comatose. The ventriculogram showed a slightly dilated ventricular system, which was symmetric on the midline as seen on the frontal anteroposterior views. The posteroanterior films (PA and Towne), however, showed gross displacement toward the midline of the left temporal horn and the posterior part of the sella media (Fig. 3).

Operation was carried out on July 27. A large left parietotemporal osteoplastic flap was turned down, and, through a parietooccipital transcortical approach, the lateral ventricle in the trigonal region was penetrated. A large lobulated tumor of firm consistency and smooth surface was encountered (Fig. 4) filling the greatly enlarged ventricular cavity. The tumor was easily dislodged from the ventricular walls, whereupon a large amount of liquid spurted out from the anterior temporal horn. Hemostasis of the tumor bed was carried out. The dura was resutured tightly. Histologically, the tumor was psammomatous endothelioma.

Immediate response after operation was surprisingly good. On the fourth postoperative day, the patient was already able to feed herself in bed. On the sixth day after operation, temperature rose to 38° C. and she was less alert; the course was constantly downhill thereafter. Bronchopneumonia was diagnosed. The patient died on the eighth postoperative day with massive pulmonary edema. No autopsy was granted.

Comment. In retrospect, we realize that insufficient attention was attached to the intraventricular calcifications, which were mistakenly interpreted as the calcified glomus of the choroid plexus. On the arteriogram (Fig. 2), a displacement upward of the sylvian group arteries was thought to result either from hemorrhage in the middle and posterior temporal lobe from a ruptured aneurysm of the posterior communicating artery, which was not visualized, or from localized brain edema.

Fig. 1. Calcification in the parietotemporal region

lobe from a ruptured aneurysm of the posterior communicating artery, which was not visualized, or from localized brain edema.

At present there is no doubt that a correct diagnosis might have been made on the strength of radiologic and angiographic findings, were it not for the acute onset of severe subarachnoid hemorrhage in a patient who had no symptoms at all previously. This misled us to search for a vascular malformation only.

Case 2. A 38-year-old woman was admitted to the Neurosurgical Department on November 21, 1958. She had been in good health until the day before admission, when her husband found her prostrate in bed in a state of mental disorientation, with severe headache and vomiting. The at-

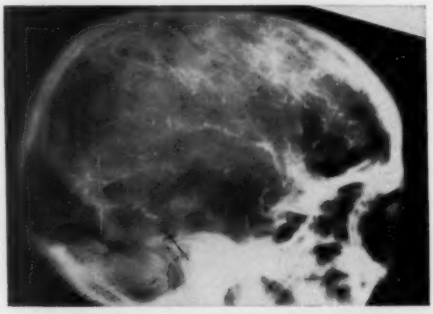

Fig. 2. Left carotid angiogram. Lateral view, arteriovenous phase. The arteries of the sylvian group are displaced upward, and their distal part in the parietotemporal region is stretched. The anterior choroid artery (*arrow*) and choroid plexus are visible.

tending physician found motor aphasia but no neck rigidity.

On admission to hospital, the patient was drowsy. She was easily aroused and made signs when talked to but did not answer intelligibly. Slight to moderate neck rigidity was noted. The pupils were equal and reacted to light stimulation. No motor deficit could be found on either side; she moved all four limbs when asked to, and there seemed to be no sensory impairment. The reflexes of the upper and lower limbs were active, the abdominal reflexes were present, and no clonus was elicited, but there was a suggestion of a positive Babinski sign on the right side. Examination of the ocular fundi showed incipient papilledema, more so on the left. The margins of the disks were blurred, and the retinal veins were engorged, but there were no hemorrhages. The visual fields and acuity could not be examined. Blood pressure was 130/80. Roentgen films of the skull did not show abnormal findings. Electroencephalographic examination (patient in stupor) recorded slow waves, 2 to 4 cps, of low amplitude over both hemispheres with a slight preponderance on the left. Lumbar puncture revealed grossly hemorrhagic cerebrospinal fluid under elevated pressure (320 mm. H_2O).

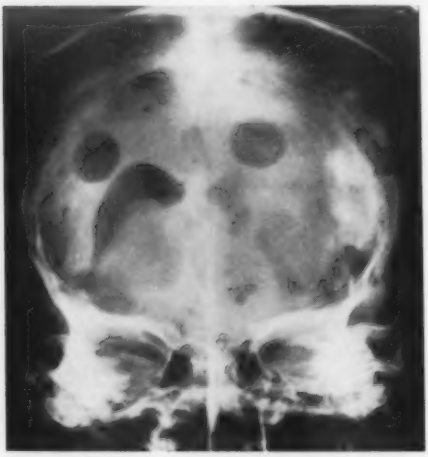

Fig. 3. Ventriculogram (posteroanterior, Towne position). A space-occupying process is delineated by the medially compressed posterior sella media and temporal horn, which are deformed, and by air trapped between the mass and the greatly distended ventricular wall of the trigone.

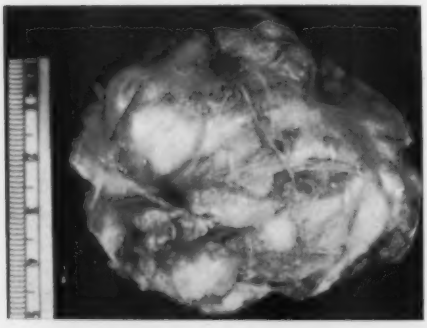

Fig. 4. The tumor of Case 1

Left-sided carotid angiograms were made because of aphasia and suspected aneurysm bleeding in the sylvian fissure. The anteroposterior films revealed noticeable arched dislocation of the anterior cerebral arteries to the right (Fig. 5). A rounded mass of pooled contrast material became visible in the late arterial (Fig. 6) and still more so in the venous phase of the angiogram (Fig. 7). The vessels of the sylvian group were elevated, and the associated peripheral arteries were generally stretched and splayed around floccular berry-sized opacifications. The anterior choroidal artery appeared much larger than the posterior communicating artery, which looked tiny in comparison. The phlebogram (Fig. 7) visualized considerable accumulation of contrast material in the trigone of the lateral ventricle. An intraventricular meningioma or gliogenous tumor growing into the lateral ventricle was suspected.

On December 3, a left parietotemporal craniotomy was performed under induced hypotension (Arfonad, Pentothal, N_2O). The trigone of the lateral ventricle was penetrated through a straight vertical incision of the cerebral cortex. A large lobulated tumor (Fig. 8) of firm consistency was easily mobilized, clipped off its feeding vessels, which derived on both ends from the choroid plexus, and extirpated. Further hemostasis was completed with coagulation and Gelfoam pledgets. The dura was closed tightly. Histologically, the tumor was typical fibroblastoma.

The patient recovered well after operation. She was still drowsy on extubation, but a few hours later she was conscious and tried to cooperate with the nursing staff. The patient had gross speech disturbances, and the right extremities were notably paretic. Blood pressure was 110/70 mm. Hg; she was afebrile, and her pulse rate was 80 per minute. Laboratory examinations of serum electrolytes before and after operation were within normal limits. Fluid intake and diuresis were controlled as usual. From the third postoperative day onward, however, the patient's general condition deteriorated. Bronchopneumonia and uremia developed, and she died four days later of circulatory insufficiency with massive pulmonary edema.

The postmortem examination showed diffuse bronchopneumonia and pulmonary edema, pleural

effusions, ulcerative tracheitis, stasis and edema of the liver, hemorrhages in the spleen, and interstitial renal edema with alterations of the tubules of the type seen in lower nephron nephrosis. The brain was not edematous, and no blood clots or other type of hemorrhage was found.

Comment. Carotid angiograms were made while the patient's condition was still serious because intracerebral hemorrhage due to rupture of an aneurysm within the left temporal lobe was suspected. It was believed that the patient's condition would not improve unless the suspected blood clot was evacuated without delay. Brain tumor was diagnosed correctly only after cerebral angiograms showed changes of the vascular pattern described[9] as consistent with the diagnosis of intraventricular meningioma.

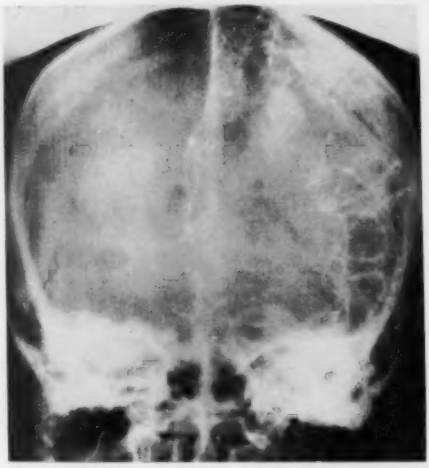

Fig. 5. Left carotid angiogram, anteroposterior view of the late arterial phase. The anterior cerebral arteries are displaced to the right. Contrast material starts pooling and demonstrates a richly vascularized lesion.

DISCUSSION

Cushing and Eisenhardt[1] differentiated between true plexus meningiomas lying wholly within the lateral ventricle and lateral meningiomas of the velum (subcortical meningiomas) partly embedded in the cerebral hemisphere. According to this criterion, in both our patients, the tumors, which were lying entirely within the ventricular cavity, were true plexus meningiomas. Both tumors were situated in the trigone of the lateral ventricle. As is usual with tumors in this location, they were easily removed after clipping and division of the large feeding vessels of the choroid plexus. One of the tumors was densely fibroblastic, while the other was characteristic of psammomatous endothelioma with calcifications visible on roentgen films. This feature is described by Cushing and Eisenhardt[1] as more common in true plexus meningiomas, which are more highly psammomatous than lateral tumors of the velum. Both patients were female and 34 and 38 years of age, respectively, near the accepted average age (32 years) at which intraventricular meningiomas manifest. Both tumors were in the left side.

In most reported cases, the duration of symptoms and signs varies from a few months to several years and headache is the first symptom. Contralateral homonymous hemianopsia, sensory-motor hemiparesis and paralexia, and symptoms suggesting cerebellar involvement may appear when the tumor compresses the posterior part of the cerebral hemisphere. Periodic attacks of severe headache are known to occur if the tumor obstructs intermittently the flow of cerebrospinal fluid. To our knowledge, subarachnoid hemorrhage has not been reported thus far in patients with intraventricular meningiomas or meningiomas

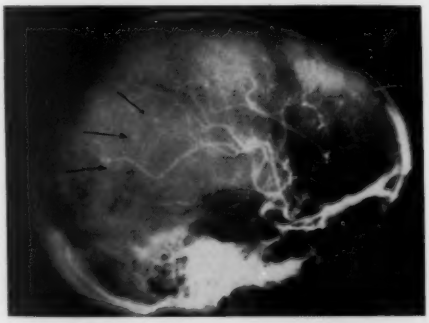

Fig. 6. Left carotid angiogram, lateral view, arterial phase. The arteries of the sylvian group are elevated, but their distal ends are abnormally stretched. The anterior choroid artery is visualized, and berry-sized poolings of contrast (*arrow*) are seen.

Fig. 7. Left carotid angiogram, Case 2, lateral view. Venous phase. Part of the tumor is visualized by abnormal pooling of contrast material. Marginal veins and tufts of abnormal small vessels give a more exact indication of its dimensions.

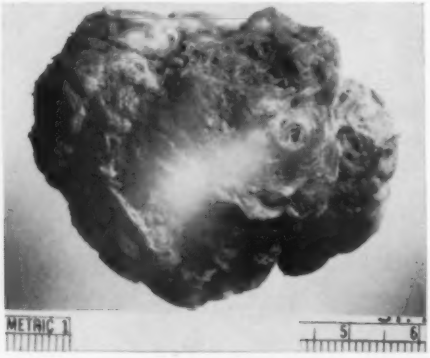

Fig. 8. The tumor in Case 2

in any other location. It seems significant that severe subarachnoid bleeding was the first manifestation in 2 of our 7 cases of intraventricular meningioma. We believe that, at least in some of the cases reported, attacks of severe headache, vomiting, diplopia, and stupor might have been due to recurrent bleeding from the vessels to the tumor. Of course, such an intraventricular bleeding cannot be excluded unless the cerebrospinal fluid was examined at the time of sudden clinical aggravation or at least before operation.

The possibility of less acute bleeding in intraventricular meningioma is illustrated by a 32-year-old man who was admitted to the Neurosurgical Department on February 26, 1957, with a history of attacks of headache and vomiting for fifteen years. These attacks were accompanied by loss of consciousness on at least 2 occasions during the previous six months. Examination showed mild disorientation, memory disturbances, left hemiparesis, and hemianoptic constriction of the left visual fields but normal fundi. Severe right posterior temporal electroencephalographic abnormality was found. Roentgen films of the skull were normal. Cerebrospinal fluid obtained on lumbar puncture for pneumoencephalographic study was xanthochromic. The pneumogram showed a right temporoparietal, space-occupying process. At operation, a large intraventricular psammomatous meningioma was removed, and old organized and more recent blood clots were found within the distended ventricular cavity. The postoperative course was uneventful from a surgical point of view. The patient was hemiplegic after operation but gradually recovered motor function of the left leg and arm. When he left the hospital on April 10, he had complete left homonymous hemianopsia. He walked and could use his left arm, although left hemiparesis was still obvious.

The mechanism of hemorrhage associated with meningioma of the lateral ventricle does not seem to be the same as that of bleeding malignant tumors, in which endothelial, obliterating vascular proliferation leads to necrosis and newly formed thin walled vessels rupture easily.[12,14,16] In these, and particularly in glioblastoma multiforme, necrosis within the neoplasm with subsequent hemorrhage is a commonly observed condition.[14] Similarly, in "pituitary apoplexy,"[18,19] the adenoma, which is ischemic because it outgrows its blood supply, compresses its own feeding vessels, which in turn results in necrosis and hemorrhage.[14] Globus and Sapirstein[15] made the interesting observation that "it is the exception rather than the rule for a tumor not to show some seepage of blood from its blood vessels into the surrounding tumor tissue." Cystic meningiomas and cysts adjacent to the tumor probably form in this pattern.[20]

The tumors recovered from our patients, however, were firmly solid, and no evidence of necrosis or hemorrhagic foci was seen on sectioning. On the other hand, it is known

that the slow growth of meningiomas is paralleled, under the demand for increased blood supply, by a corresponding enlargement of feeding arteries, which become tortuous and less resistant to blood pressure change. It is assumed that the intraventricular location of these pathologic vessels favors their rupture in the same manner as aneurysms, and vascular malformations tend to bleed under stress into the subarachnoid space. In this regard, we should like to recall Dandy's statement[21] that it is "a fairly safe but not absolute rule that when cerebral hemorrhage occurs during youth or middle age i.e. before the time when vascular accidents are to be expected, there must be an underlying tumor or aneurysm, either of which will contribute defective vessels."

SUMMARY

Case reports on 2 patients whose illnesses started abruptly with severe subarachnoid hemorrhage associated with plexus meningioma of the lateral ventricle are presented.

The acute onset of headache, vomiting, stupor, and neck rigidity in these young patients, who had no previous symptoms, seemed to indicate aneurysmal origin of the hemorrhagic cerebrospinal fluid obtained on lumbar puncture. Carotid angiograms were made in both patients.

Although hemorrhage with meningioma of the lateral ventricle seems not to have been reported in the literature, the authors believe that its occasional occurrence is probably responsible for clinical aggravation in some cases. In addition to acutely manifesting massive bleeding into the subarachnoid space, a second form is reported in which recurrent exacerbations thought to result from intermittent obstructive hydrocephalus were in fact due to repeated self-limiting bleeding from pathologic vessels within the ventricular cavity. This was confirmed in one of the authors' cases by the finding of xanthochromic cerebrospinal fluid on lumbar puncture and of organized blood clots adjacent to the tumor at operation. It is possible, at least in some of the cases of meningioma of the lateral ventricle with recurrently aggravating manifestations reported in the literature, that such a less acute form of bleeding occurred and that its rarity is more apparent than real.

The mechanism of hemorrhage is briefly discussed.

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Neurologic aspects of temporal arteritis

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Henry P. Wagener, M.D., and Richard M. Shick, M.D.

In the years 1931 to 1959, 175 patients with temporal arteritis were seen at the Mayo Clinic. At least 111 of these patients were referred to the Clinic with symptoms or signs suggesting possible involvement of the central nervous system, and 88 were seen primarily or in consultation by a neurologist at the Clinic. The referring physicians sent 41 patients because of headaches, 37 because of blindness, and 4 because of diplopia without any specific diagnosis. Brain tumor was suggested in 11, trigeminal neuralgia in 8, meningitis in 2, subarachnoid hemorrhage in 2, "stroke" in 2, histaminic cephalgia in 2, pituitary cyst in 1, and other diseases in 52 (Table 1). Only 13 patients were referred with conditions already diagnosed specifically as temporal arteritis.

Although temporal arteritis is seemingly rarely fatal, at least in the United States, it is often incapacitating. The importance of establishing the diagnosis rapidly can be appreciated when it is realized that 42% of the patients seen at the Clinic became blind in one or both eyes before diagnosis was made, even though loss of sight might have been prevented by early adequate steroid therapy.

TABLE 1
REFERRING PHYSICIAN'S DIAGNOSIS IN 175 CASES OF TEMPORAL ARTERITIS

Diagnosis	*Cases*
Temporal arteritis	13
Headache	41
Blindness	37
Brain tumor	11
Trigeminal neuralgia	8
Subarachnoid hemorrhage	2
Meningitis	2
Stroke	2
Histaminic cephalgia	2
Diplopia	4
Mandibular joint arthritis	8
Metastatic neoplasm	8
Fever of undetermined origin	8
"Swollen lumps"	5
"Ear" or "tooth" trouble	5
Whiplash injury	1
Pituitary cyst	1
Miscellaneous	17

GENERAL CONSIDERATIONS

The literature on the syndrome of temporal arteritis is by now voluminous, and no attempt will be made to review it in detail. In the modern literature, the first unmistakable case to be reported is that of Hutchinson[1] in 1890. Schmidt[2] described a typical case in 1931, although he made the mistaken diagnosis of aneurysm of the right internal carotid artery. In the Tadhkirat of Ali ibn Isa[3] of Baghdad, who lived from about 940 to 1010, the twenty-fifth chapter concerns excision of arteries and their cauterization. He stated, "By these means one treats not only migraine and headache in those patients that are subject to chronic eye disease, but also acute, sharp, catarrhal affections, including those showing heat in and inflammation of the temporal muscles. These diseased conditions may terminate in loss of eyesight; frequently they are attended by a considerable degree of chemosis." It seems possible that this brilliant observer may have had experience with temporal arteritis.

Horton, Magath, and Brown[4] first defined the syndrome of temporal arteritis as a clinical entity in 1932. Since then, many excellent reviews[5–9] have appeared. A number of papers describe the cases encountered at the Mayo Clinic.[10–25] The present paper concerns all patients with diagnoses of temporal arteritis who have been seen at the Mayo Clinic since 1931. Papers pertaining in greater detail to the visual aspects are those of Bruce,[7]

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Wagener,[17] Wagener and Hollenhorst,[25] and Palm.[26]

The cause of this disease is still obscure, despite a good deal of theory and conjecture over the years. Although it has a predilection for the arteries of the carotid system, it is now generally agreed that temporal arteritis is not a disease limited to the temporal arteries, or even to the cranial vessels, but may involve major branches of the aortic arch and other large arteries also. For these reasons, terms such as "cranial arteritis"[6] and "giant-cell chronic arteritis"[5] have been proposed but have not replaced the commoner designation, "temporal arteritis." Patients with widespread vascular involvement have, as a rule, had slightly atypical changes in the arteries, and, usually, the pathologist has been hesitant about definitely identifying the condition of the arteritic lesions as temporal arteritis.

Arteries affected by temporal arteritis are usually much larger than those involved in periarteritis nodosa. The lumen of the affected artery is usually reduced to a slit because of severe intimal thickening (Fig. 1). Foci of inflammatory cells and giant cells are found in the intima and media, with focal necrosis and granulomatous formation near the elastic lamella. Often, there are foci of hemorrhages. The internal elastic lamina may be necrotic, fragmented, or reduplicated, and the giant cells tend to engulf elastic tissue. Spotty perivasculitis of the vasa vasorum and, sometimes, phlebitis of the venae comitantes develop. Edema and pain are caused by fibrosis about the vessels and nerves.

The prognosis for life seems to be extremely good, although fatal termination has been reported in a few cases. Reports of these cases are included in the articles by Gilmour,[5] Wagener and Hollenhorst,[25] Cardell and Hanley,[27] and Lavy and Liban.[28] In each case in which the patient died, there is some doubt that the disease was actually temporal arteritis, since the pathologic picture was atypical.

In its fully developed form, temporal arteritis is relatively easy to diagnose. However, in its early stages, before the superficial vessels are clinically affected, a definite diagnosis may be impossible to make. Occasionally, the most dreaded complication, loss of vision, may be the first symptom.

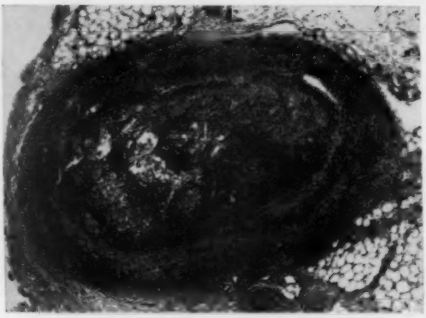

Fig. 1. Histopathology of temporal arteritis. Severe intimal proliferation, foci of inflammatory cells, and giant cells in intima and media. Hematoxylin and eosin. Reduced from × 65

Temporal arteritis affects mainly persons 55 years of age or older, although the patient of Meyers and Lord[29] was 22, one of Gilmour's[5] patients was 23, and Hass'[30] patient was 19 years of age. None of these patients had entirely typical findings, and none had ocular involvement. An 18-year-old girl seen at the Clinic but not included in this series had periarteritis nodosa involving the temporal arteries. A 28-year-old Negro observed by Harrington[31] was said to have typical temporal arteritis.

In a few patients, the disease has an explosive onset with severe headaches. The temporal or occipital arteries may be hard, nodular, red, and tender, and there may be signs of severe systemic inflammatory disease. In the majority of patients, however, onset is insidious, with fatigue, anorexia, night sweats, loss of weight, low grade fever, and diffuse aching in the muscles of the neck, chest, or scalp. Aching also may be noted in the knees, shoulders, or hips. These symptoms might well indicate a prodromal period; during this time, many patients consider themselves afflicted by "the flu," and correct diagnosis is rarely possible.

The prodromal period may last from several weeks to three or four months. The headache, although sometimes mild or absent, usually gradually increases in severity. The patient often describes headache and superficial tenderness in the scalp, which varies from a constant dull ache to sharp lancinating pains, sometimes excruciating and almost unbearable.

It is usually worse in the evening or at night and is aggravated by the slightest touch and especially by exposure to cold. The patient may call attention to tender areas or even reddened nodules on the scalp. The scalp may be so tender that combing the hair or wearing a hat may be impossible. The muscles in the neck may be extremely tender and may prevent the patient from bending or turning his head. Intermittent claudication of the muscles of mastication or severe trismus is a common symptom; the patient may call this "lockjaw." The carotid arteries also may be unusually tender to palpation.

Excessive elevation of the erythrocyte sedimentation rate is usual in the early stages; it is commonly more than 100 mm. in one hour (Westergren method). Mild hypochromic anemia is often present, and slight leukocytosis and occasional changes in the electrophoretic pattern of the blood serum may develop. Usually, the blood smear shows striking rouleaux formation and a shift of the leukocytes to the left.

The major and severest complication of the disease is the loss of vision which results from impaired blood supply to the optic nerve or retina. The eyes may be affected in 3 ways: [1] by ischemic optic neuritis, [2] by ischemic retrobulbar neuritis, or [3] by occlusion of the central retinal artery. In ischemic optic neuritis, the optic disk is swollen and pale. Fragmentation of the blood stream may occur in one or more of the vessels, and, often, ischemic patches or hemorrhages develop in the adjacent retina. This is the most frequent form of ocular involvement. The visual loss may be partial or complete. In ischemic retrobulbar neuritis, loss of vision develops without observable change in the retina or optic nerve. In occlusion of the central retinal artery, pale ischemic edema of the retina and a cherry-red spot in the macula are associated findings.

Many patients with temporal arteritis have mild mental depression, and some are mildly confused or disoriented. These manifestations may be expressions of toxicity but, in some cases, may be due to cerebral arteritic changes.

PRESENT SERIES

Of the 175 patients in this series, 95 were women and 80 were men. One patient was 50 years of age, one 53, one 54, one 57, two 58, and one 59; the remainder were 60 years of age or older. All but 57 of the patients have been seen since 1952. During the past seven years, from 14 to 21 new patients with this disease have been seen yearly at the Clinic. Biopsy in 113 of the 175 patients showed positive findings, and in 8 the findings were negative. Biopsy was not performed on 54 patients; either the diagnosis was certain or the patient refused the operation.

The majority of patients in this series noted systemic symptoms such as weakness, fatigue, malaise, loss of weight, low grade fever, night sweats, and anorexia for two weeks to four months before their examinations at the Clinic. Most patients also had mild to severe headaches or had a history of such symptoms. Many still experienced aching of the muscles of the extremities, neck, and shoulders.

Most patients in this series had thrombotic or nodular temporal, posterior auricular, or occipital vessels. However, several had apparently normal, pulsatile temporal arteries. In some cases, although the vessels were considered normal clinically by the examining physician, the results of biopsy were positive. In 83 of the 175 patients, the presence of intermittent claudication of the jaw, weakness and pain in the jaw, difficulty in swallowing, or mild to severe trismus was noted; 17 patients had a palpable thrombotic facial artery on one or both sides.

Laboratory findings. The most important laboratory finding was extreme elevation of the erythrocyte sedimentation rate. This test proved to be a most important diagnostic aid (Fig. 2). Most of the patients had an erythrocyte sedimentation rate in excess of 70 mm. in one hour (Westergren method). Patients treated with cortisone or other steroids before admission had significantly lower sedimentation rates, and the results for such patients are not included in Figure 2.

Hypochromic anemia was usually mild, although it sometimes was severe (Fig. 3). Smears of peripheral blood almost always showed advanced rouleaux formation, and many showed evidences of hypochromasia in the red cells and toxic changes in the white cells. Often mild leukocytosis had developed, the number of leukocytes ranging from 9,000

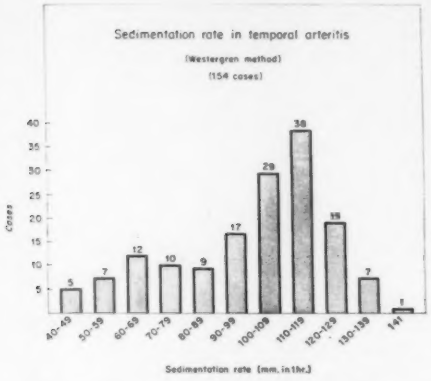

Fig. 2. Sedimentation rate in temporal arteritis (Westergren method); 154 cases

to 17,000 per cubic millimeter of blood. Several patients had mild eosinophilia with 1 to 3% eosinophils. One patient had positive results for the Bence Jones test for protein, and electrophoretic studies of the blood serum in another patient showed significant elevation of the globulin fraction.

Ocular signs. The nature of the ocular involvement is shown in Table 2. Only 68 patients (about 40%) were completely free of ocular signs and symptoms associated with temporal arteritis. Of these, 4 had ocular lesions not related to temporal arteritis: 2 had venous occlusions in one eye, 1 had vitreous hemorrhages in one eye, and 1 had hypertensive retinopathy in both eyes. Excluding these 4 cases, 102 patients (58%) had some form of ocular involvement resulting from temporal arteritis; 73 of the patients (42%) permanently lost part or all of their vision, 21 (12%) were completely blind in both eyes at the time of dismissal, and 34 had a history of transient visual loss (amaurosis fugax) in one or both eyes. Half the patients in the last group later sustained permanent loss of vision.

The patient could rarely be sure of the time of onset of the disease. However, we have attempted to determine how long after onset the loss of vision occurred (Table 3). This is of some importance in calculating how long to treat the patient. In a third of the patients, loss of vision occurred within two to three months; in none did it occur more than ten months after onset of disease.

Double vision was noted by 22 patients. In 12 of these, we did not find muscular imbalance, but 10 had demonstrable lesions of the extraocular muscles. Of the 22, 10 later lost vision in one or both eyes; 2 others had attacks of amaurosis fugax but no loss of vision. Evidences of retinal ischemia, as manifested by cotton-wool patches in both eyes, were found in 4 additional patients. Of these, 2 had had amaurosis fugax, but the others were unaware of visual difficulty; 2 other patients had cotton-wool patches in one eye, with no visual symptoms.

The ophthalmoscopic findings in our group of cases are listed in Table 4. Ischemic optic neuritis was the lesion responsible for the loss of vision in 86 eyes. In each of these eyes, the optic nerve was slightly pale with edema along its margins (Fig. 4). Sometimes edema elevated the disk 1 or 2 diopters. Usually, one or more small cotton-wool patches in the retina were associated with edema of the disk. The blood column in the veins or arterioles was often fragmented, or marked rouleaux formations were seen. Frequently, small hemorrhages had occurred in the retina. Normal ophthalmoscopic appearance was noted in 6 eyes from which all or part of the vision had been lost. Probably, the arteries within the

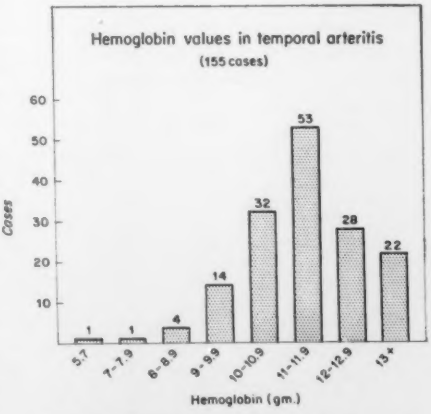

Fig. 3. Values for hemoglobin in 155 cases of temporal arteritis

TABLE 2
OCULAR INVOLVEMENT IN 175 PATIENTS WITH TEMPORAL ARTERITIS

		Patients
No ocular signs or symptoms		68
Visual defects:		73
Blind		
Both eyes	21	
One eye; partial loss of other eye	14	
One eye; other eye normal	11	
Partial loss of vision		
Both eyes	13	
One eye	14	
Amaurosis fugax:		34
Preceding permanent loss of vision	17*	
With no subsequent loss of vision	17†	
Diplopia:		22
Demonstrable muscle paresis	10‡	
History only	12§	
Cotton-wool exudates in retina but no ocular symptoms		6

*These patients are included in the 73 with visual defects; 1 had diplopia also.
†1 had diplopia also.
‡4 patients who later lost vision are included in the 73 with visual defects.
§6 patients who later lost vision are included in the 73 with visual defects.

optic nerve were involved in these cases. Retinal changes characteristic of occlusion of the central artery, that is, ischemic edema of the retina and a cherry-red spot at the macula, were found in 3 eyes. One patient sustained occlusion of the central artery and vein in one eye and had ischemic optic neuritis in the other; 19 eyes had pale atrophic optic disks and belonged to patients in whom the visual loss had occurred a week or more before our examination (Fig. 5). Ischemic retinopathy, consisting of cotton-wool patches in the retina with or without associated visual defects, was noted in 10 eyes. Figure 6 shows a number of representative field defects among patients who lost only part of their vision.

NEUROLOGIC INVOLVEMENTS

Many authors, particularly Gilmour,[5] Kilbourne and Wolff,[6] Cooke and associates,[8] Cardell and Hanley,[27] Lavy and Liban,[28] Schaefer and Sanders,[32] Bowers,[33] Sprague and MacKenzie,[34] and Bain,[35] have pointed out that arteries other than those of the carotid system may be involved. In this series, 88 patients were seen in consultation by a neurologist because of headaches, blindness, and other symptoms that often suggested the presence of an intracranial lesion. The electroencephalographic findings in 20 patients with temporal arteritis showed that 12 patients had no abnormalities, 6 had bisylvian dysrhythmia (grade 2), 1 had diffuse dysrhythmia in the right sylvian region, and 1 had transient dysrhythmia in the left sylvian region. The results of neurologic examinations in 69 of the 88 patients were completely normal. The relative rarity of neurologic changes is striking.

The positive findings on examination of the nervous system listed briefly in Table 5 are difficult to classify, and, indeed, it is not possible to determine their relationship to temporal arteritis with any degree of certainty except in so far as their chronology is concerned. One patient had suffered epileptic seizures for fourteen years before onset of the disease. Another patient in whom an acute mania developed during steroid therapy had had advanced senile dementia for some years before onset of arteritis. Right homonymous hemianopsia developed in 1 patient a year before onset of symptoms of temporal arteritis. In 2 patients with crossed-leg palsy and 1

TABLE 3
ESTIMATED DURATION OF TEMPORAL ARTERITIS BEFORE LOSS OF VISION OCCURRED

Duration	*Number of patients*	*Interval between visual loss in one eye and visual loss in second eye*	*Number*
No prior symptoms	1	Same time or unknown	25
3 days	1	1 day	5
4 days	1	2 days	2
1 week	1	3 days	2
2 weeks	6	4 days	2
3 weeks	8	5 days	1
4 weeks	9	7 days	5
5 weeks	5	9 days	1
6 weeks	8	2 weeks	1
7 weeks	0	3 weeks	2
2 months	11	4 weeks	2
3 months	11		
4 months	2		
5 months	2		
6 months	3		
7 months	3		
10 months	1		
Total	73	Total	48

TABLE 4
OPHTHALMOSCOPIC FINDINGS IN 127 EYES OF 175 PATIENTS WITH TEMPORAL ARTERITIS

	Eyes	*Bilateral involvement*
Ischemic optic neuritis	86*	30 patients
Ischemic retrobulbar neuritis (normal fundus)	6	2 patients
Occlusion:		
Of central artery	3	1 patient
Of central artery and vein	1	
Optic atrophy	19	8 patients
Ischemic retinopathy	10†	4 patients
Visual loss; eyes not examined	2	1 patient
Total	127	46 patients

*One patient had ischemic optic neuritis in one eye but old occlusion of the central vein in the other.
†One patient had right homonymous hemianopsia and ischemic retinopathy of the right eye. Ophthalmoscopic examination of left eye showed it to be normal.

with a right Babinski sign and downward nystagmus, onset of these changes was evident some months before temporal arteritis developed.

Systemic abnormalities that coincided with or followed closely onset of temporal arteritis probably were related to temporal arteritis; 1 patient had several episodes of fainting or convulsions, 1 had acute loss of hearing of unknown cause but later improved, and 2 had weakness of one arm thought to be of either myositic or neuritic origin. Angina pectoris developed in 1 of the latter patients; 1 patient had acute hemiplegia a few weeks after leaving our care. Another died of massive cerebral hemorrhage two weeks after leaving.

The patient who was found at necropsy to have had disseminated periarteritis nodosa had an unusual and not completely typical giant cell granulomatous reaction about the right temporal artery.[25] Peripheral neuritis and right hemiplegia developed later.

The remaining 6 patients are of unusual interest, although lack of necropsy data makes it impossible to be entirely sure of the anatomic diagnosis. In these cases, the aortic arch or its branches may well have been involved. It should be noted that Palm[26] reported the cases of 2 patients with temporal arteritis in whom angiograms disclosed narrowing of the internal carotid artery. Also, Heptinstall, Porter, and Barkley,[36] in a case in which necropsy was performed, found typical histologic changes in the common carotid arteries. One of our patients was a 72-year-old man in whom an illness developed in mid-October 1956, causing malaise, anorexia, fever, diplopia, and severe frontal headaches. The referring physician found almost complete paralysis of the left lateral rectus muscle. Eleven days later, the patient began to lose the vision of the right eye. Examination at the Clinic on October 23 showed visual acuity of only 8/300, right eye, and 20/40, left eye. The right eye showed signs of ischemic optic neuritis, but the fundus of the left eye was normal. Incongruous left homonymous hemianopsia was found (Fig. 7). Neurologic examination showed slight ataxia of the upper and lower extremities and a questionable Babinski sign on the right. Electroencephalograms on October 27 showed dysrhythmia in the left sylvian region. Two weeks later, the electroencephalogram was normal. Biopsy of the temporal artery showed typical temporal arteritis.

Involvement of arteries in the carotid system other than the temporal and ophthalmic arteries, without definite neurologic findings, was evident in 2 patients who had tender common carotid arteries and occluded facial arteries; 1 of these patients had acute labyrinthitis and died ten years later of dissecting

Fig. 4. Ischemic optic neuritis in left eye of patient with temporal arteritis. Pallor and edema of the disk developed two days after onset of the disease with fragmentation of the arteriolar blood column.

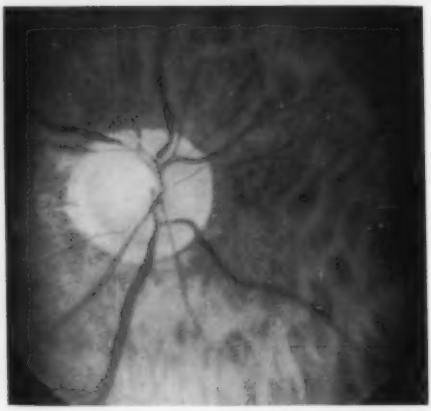

Fig. 5. Right optic disk with moderate atrophic pallor in a patient blind four months from temporal arteritis. The retinal vessels have normal caliber.

aortic aneurysm. Specific involvement of vessels outside of the carotid system was found in 3 of our patients; 1 of these had Raynaud's phenomenon and occlusive arterial disease of the left arm and both legs, the second had an occluded left radial artery with histologic lesions typical of temporal arteritis in a section obtained at biopsy, and the third had transient left homonymous hemianopsia, vertigo, and absence of a radial pulse in both arms.

Diplopia. Because of their complaints of diplopia, 22 patients presented unusual diagnostic problems; 12 did not have demonstrable extraocular muscle abnormalities at the time of examination, and the 10 who did have definite extraocular muscle involvement had variable abnormalities. Only 1 patient had paresis of the lateral rectus muscle. The other 9 had involvement of the vertically acting muscles of one or both eyes. Reports of 2 cases will illustrate the rapidly changing character of the extraocular muscle involvements.

Case 1. A 68-year-old farmer registered at the Clinic on April 11, 1953, because of headaches. His health had been good until February 28, when he had cleaned his fireplace; he had noted nasal stuffiness thereafter. The next day, a dull frontal headache developed. On March 2, the vessels in the temporal scalp became prominent, and he noted sharp twinges of pain in these areas. His scalp became so painful he could not comb his hair. He lost his appetite and complained of night sweats and weakness; 6 chiropractic treatments were without avail. On March 15, his jaws became sore and he could not open his mouth to eat or talk. He was hospitalized on March 31 and received diathermy, massage, neck traction, and pain tablets. April 2 marked the onset of diplopia.

On April 11, when he was seen at the Mayo Clinic, the results of examination were essentially negative except for weakness of muscles supplied by the left third nerve and thrombotic nodular temporal arteries. By the next day, extraocular muscle involvement had changed and only paralysis of convergence remained. The same afternoon, the findings changed again to paresis of both medial rectus muscles and the right lateral rectus muscle and nystagmoid movements of the eyes on extreme gaze to the right. Overaction of both inferior oblique muscles and mild paresis of the left inferior rectus muscle were also noted. These findings aroused considerable discussion as to the possible location of the responsible lesion.

On the following day, the muscle paralysis had changed again and both medial recti, the left inferior rectus, and the levator of the left eye were paralyzed. Biopsy of the temporal artery showed temporal arteritis, and treatment with cortisone was begun immediately. All symptoms except diplopia completely disappeared within a few days; diplopia too was gone two months later.

Case 2. A 65-year-old druggist reported to the Clinic on September 8, 1954, with symptoms essentially similar to those mentioned in Case 1. He had mild ptosis of the right upper lid and moderate paresis of the superior oblique, medial rectus, and inferior rectus muscles of the right eye. On September 14, biopsy of the temporal artery

TABLE 5

NEUROLOGIC LESIONS IN 175 PATIENTS WITH TEMPORAL ARTERITIS

Results of neurologic examination		*Patients*
Normal		69
Abnormal		19
Abnormalities and their relation to temporal arteritis:		
Probably unrelated	6	
Epilepsy	1	
Acute mania	1	
Right homonymous hemianopsia	1	
Crossed-leg palsy	2	
Right Babinski sign and nystagmus	1	
Probably related	13	
Episodes of fainting or convulsions	1	
Acute loss of hearing	1	
Brachial neuritis (?) or myositis with upper limb paresis	2	
Massive cerebral hemorrhage and death	1	
Stroke several weeks later	1	
Right hemiplegia, right homonymous hemianopsia, peripheral neuritis, periarteritis nodosa, and death	1	
Possible occlusive disease of aortic arch	6	

gave positive results for temporal arteritis and cortisone therapy was begun. The systemic symptoms immediately subsided, and his diplopia lessened; six days later, he had diplopia only on upward gaze. By September 27, he was free of it.

The shifting nature of the paresis of the ocular muscles in these 2 and the other patients with diplopia suggests strongly that the lesion responsible was ischemia of the nerves supplying the extraocular muscles in the orbit or of the muscles themselves. Findings were too bizarre to have been due to central nervous system involvement.

TREATMENT

Blindness is the most dreaded complication of temporal arteritis. Most authors have stated that approximately 50% of patients become blind in one or both eyes. The earlier the diagnosis is made and treatment with steroids is begun, the lower will be the incidence of blindness. Because the danger of visual loss is so great, it has been our policy since October 1949 to treat as emergency patients all patients with temporal arteritis who are not completely blind and to give them cortisone or one of the related adrenocorticosteroids even if the eyes are not involved at the time of admission. As a rule, treatment is begun before biopsy if any delay in this procedure is anticipated. Only one of our patients lost vision after this therapy was started. The dosage of 100 mg. of cortisone daily was inadequate for this patient. In this series, 104 patients were treated with cortisone or one of the other adrenocorticosteroids, and 17 of these patients received anticoagulant therapy also. The remaining patients either were not treated or were treated with heparin, penicillin, or other substances before October 1949, when steroids were first employed.

We prefer the intramuscular route of administration of cortisone for the first week or so of treatment because of the high sustained level of dosage this produces. Usually, 300 mg. of cortisone is given intramuscularly on the first day of treatment; for the first week or ten days, 150 to 200 mg. is given daily by the intramuscular route or changed over to the oral method when the erythrocyte sedimentation rate has begun to return toward normal levels. A total dosage of 150 to 200 mg. daily should be continued for four to six weeks

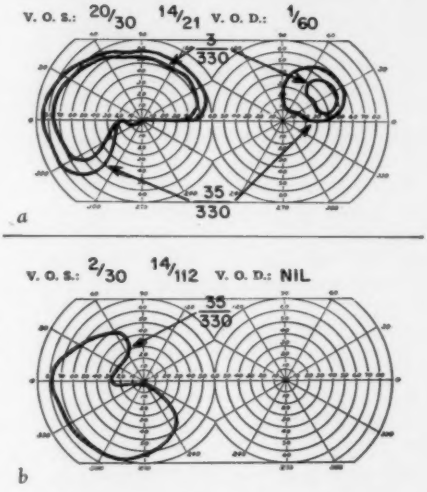

Fig. 6. *[a and b]* Types of visual field defects produced by temporal arteritis involving both eyes

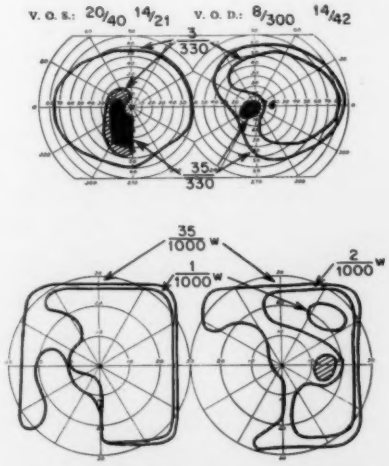

Fig. 7. Visual fields of patient with temporal arteritis, ischemic optic neuritis of right eye, normal fundus of left eye, and incongruous left homonymous hemianopsia

before the amount is gradually reduced. After six weeks, the amount is gradually decreased to between 50 and 75 mg. daily for three to four months. We have not considered it necessary to use anticoagulant therapy routinely. Before the advent of steroids, a number of patients were treated with anticoagulant drugs alone; this medication did not seem to prevent further visual loss. At least theoretically, there may be advantages to the use of anticoagulants combined with steroids when a patient has recently lost vision in one eye and, consequently, involvement of the other ophthalmic artery is a possibility. The intermittent inhalation of 100% oxygen has been of benefit in patients with recent visual impairment. The use of vasodilators such as histamine or acetylcholine probably is contraindicated, since, in the years preceding the use of cortisone, several patients had increased visual loss shortly after such drugs were employed. This effect may have resulted from a diminution in systemic blood pressure and may have led to greater ischemia of the visual system.

SUMMARY AND CONCLUSIONS

The clinical findings in 175 patients with temporal arteritis are summarized; 42% lost vision in one or both eyes, and 12% had diplopia. If one excludes paresis of the ocular muscles, the incidence of objective neurologic or electroencephalographic findings was exceedingly low; the abnormalities that were present probably resulted from involvement of the intracranial or aortic arch arteries. It is concluded that early therapy with adrenocortical steroids is urgently indicated and should not be delayed.

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Experimental study of the effects of hypothermia on local brain injury

E. J. Laskowski, M.D., I. Klatzo, M.D., and M. Baldwin, M.D.

OVER THE PAST few years, hypothermia has become an accepted procedure, primarily in cardiac and neurologic surgery. With regard to cardiac surgery, the most important effect of hypothermia is related to the increased tolerance of the brain to ischemia resulting from interrupted circulation. Rosomoff[1] and Pontius and DeBakey[2] have demonstrated that the ischemic necrosis in the brain due to occlusion of its arterial blood supply can be almost completely prevented in hypothermic animals. In neurologic surgery, a further beneficial effect of hypothermia is assumed to derive from the reduction of cerebral edema. Pertinent to this problem, observations of Rosomoff and Gilbert[3] indicate that, in hypothermic dogs at 25° C., the brain volume is reduced 4.1% and the available intracranial-extracerebral space is increased 31.8%. With respect to the effect of hypothermia on the permeability of the blood-brain barrier, Jeppson and Nielsen[4] found that the number of lesions caused by injury to the blood-brain barrier with 50% Diodrast declined sharply with the reduction of cerebral temperature.

Cerebral edema with its relationship to the permeability of the blood-brain barrier and the behavior of the tissue elements has been studied recently by our group.[5] In the course of these investigations, it was found possible to make a highly reproducible brain lesion, the dynamics of which could be followed chronologically. This lesion consisted essentially of a saucer-shaped, sharply demarcated necrosis of the superficial layers of the cortex and an area of edema in the white matter of the underlying gyrus. The chronologic observations on this area of edema, in which no apparent destruction of tissue elements was produced, revealed a close relationship among the development of edema, alteration of blood-brain barrier, and behavior of astrocytes. One of the main implications from this study was that the astrocytes are primarily involved in the process of cerebral edema.

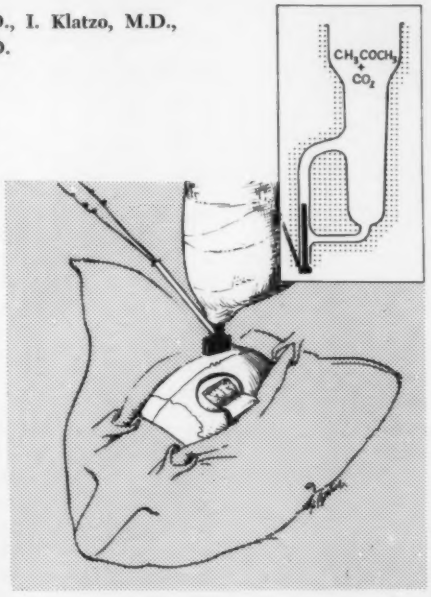

Fig. 1. Technic of the cortical cold injury. The stem of the metal plate is inserted into the glass container in which a mixture of dry ice and acetone is circulating. The microthermistor provides the exact temperature reading of the plate.

In order to elucidate the effects of hypothermia on cerebral edema, it appeared that a comparative study of normothermic and hypothermic animals subjected to the previously

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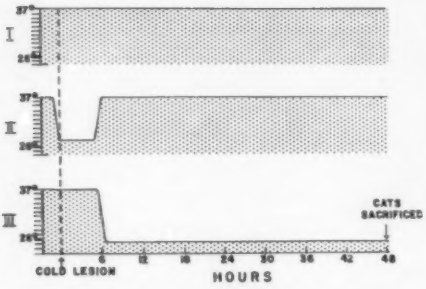

Fig. 2. Experimental animals. Group I: cold lesion without hypothermia; group II: cold lesion produced in hypothermia continued for six hours; group III: hypothermia induced six hours after cold injury and continued for forty-two hours, at which time the cats were sacrificed.

described standardized lesion would reveal the manner in which some basic aspects of edema may be significantly modified by the lowered body temperature.

MATERIAL AND METHODS

The apparatus used for the production of the brain lesion consisted basically of a stainless steel plate with a 4 x 10 mm. surface. The stem of this plate was mounted into a system of glass tubing in which a mixture of dry ice and acetone was circulated (Fig. 1). A microthermistor imbedded below the plate's surface provided accurate temperature measurement. Assessment of the temperature changes in the depths of the brain during and after application of the cold plate was made by thermistors at levels 2 and 5 mm. below the cortical surface to which the plate was to be applied.

Cats anesthetized with intraperitoneal Nembutal were operated upon under aseptic conditions. Through a 15-mm. trepine opening, the pial surface of the left medial suprasylvian gyrus was exposed. The surface of the plate was brought consistently to −50° C. and then placed in light contact with the exposed pial surface of the cortex for twenty seconds. The time application of twenty seconds was arbitrarily chosen because the consequent injury did not endanger the life of an animal yet produced a consistently sizable lesion. A few drops of Elliott's solution at 37° C. quickly released the frozen plate from the cortical surface. Complete closure of the dura and overlying structures concluded the operation.

For the blood-brain barrier studies, 2 cc. of 10% sodium fluorescein was administered intravenously forty-five to sixty minutes before sacrifice by decapitation of the animal. The brains were photographed in ultraviolet light immediately after removal and sectioning in the coronal plane through the center of the lesion.

After photography, the brains were fixed in preparation for the numerous histologic and histochemical technics. These included cresyl violet stain, hematoxylin and eosin, Gomori's trichrome, Heidenhain and luxol blue for myelin, Holmes' for axons, Cajal's gold chloride for astrocytes, Penfield's modification of Hortega's for oligodendroglia and microglia, Lepehne-Pickworth benzidine method, and periodic acid–Schiff (PAS) technic. For histochemical analysis of PAS-positive material, the following procedures were used: inhibition with acetylation method (Gersh), incubation in diastase and hyaluronidase (streptococcal and bovine), thionine and methylene blue stains for metachromasia, methylene blue extinction test (Dempsey and Singer), Millon reaction, and Sudan black B stain.

The effects of hypothermia on the experimental brain lesion were assessed in 3 groups of animals (Fig. 2). Group I served as a control, and the temperature of these animals was maintained at 37° C. during and after the surgical procedure. These cats were sacrificed in groups of 6 animals each at time intervals as follows: immediately after the surgical procedure; six, twelve, twenty-four, forty-eight, and seventy-two hours; and seven, thirty, sixty, and ninety days postoperatively.

In Group II, the temperature of the animals was lowered to 28° C. (rectal) before application of the lesion and maintained between 26 to 28° C. for six hours before warming and return of the cats to their cages. Of these, groups of 6 animals each were sacrificed at twenty-four, forty-eight, and seventy-two hours and seven days after brain injury.

Hypothermia was induced by covering the body and extremities with plastic ice bags, and warming was accomplished with electric heat-

ing pads. Temperatures were recorded at ten-minute intervals by a thermocouple in the rectum and a microthermistor in the white matter of the parietal region, opposite the operative site. When the rectal temperature reached 26 to 28° C., the cold plate was applied. The dura and remaining structures were closed immediately. Subsequently, the animals were maintained at rectal temperatures of 24 to 28° C. for periods of six hours after application of the cold plate. Figure 3 shows the temperature records of a typical animal from this group.

Group III is represented by 10 animals in which rectal temperatures were maintained at 37° C. until six hours after production of the cold lesion and then lowered to 25 to 26° C. for the remainder of forty-eight hours, at which time the cats were sacrificed.

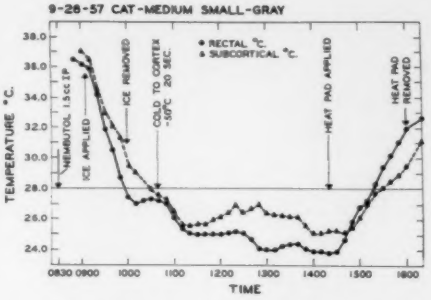

Fig. 3. Temperature record of an animal from group II

OBSERVATIONS

Temperature recordings within the brain taken during and after application of cold are presented in Figure 4. The temperature of the plate rose during the twenty seconds of application from −50 to −20° C. The temperature drop at 5-mm. depth, which corresponds to the white matter at the base of a gyrus, was approximately equal in normothermic and hypothermic animals and amounted to 10°. A more significant difference was recorded at 2-mm. depth, which corresponds approximately to the borderline between the cortex and the white matter. At this depth, the normothermic animals showed a drop of 16° as compared with a 25° drop in the hypothermic animals. Return to initial temperatures was similar in both groups of animals, the recovery pattern being somewhat slower in the hypothermic animal.

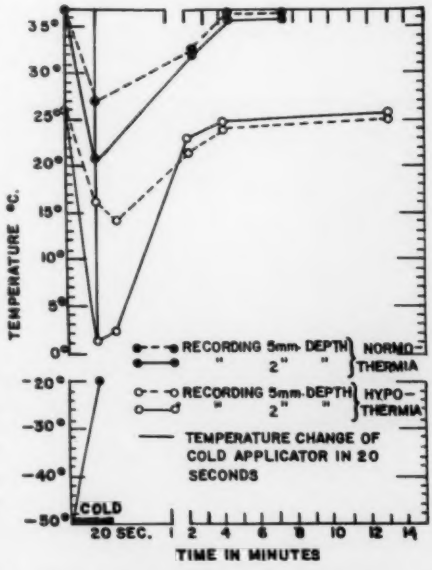

Fig. 4. Average intracranial temperatures recorded during and after application of the cold plate in normothermic and hypothermic animals

Since the various stages of our experimental lesion have been already reported in detail,[5] the present observations are confined to features that revealed significant differences between normothermic and hypothermic groups.

In normothermic animals, the maximum edema in the white matter was reached at twenty-four hours postoperatively. The cortical lesion was marked by a sharply demarcated necrotic zone involving the superficial layers of the cortex. The underlying white matter presented the picture commonly associated with edema. In myelin preparations, there was a pallor due to a separation of the myelinated fibers without any histologic evidence of myelin disintegration. Sections stained with PAS revealed, in the edematous area, an intense PAS-positive staining of greatly swollen astro-

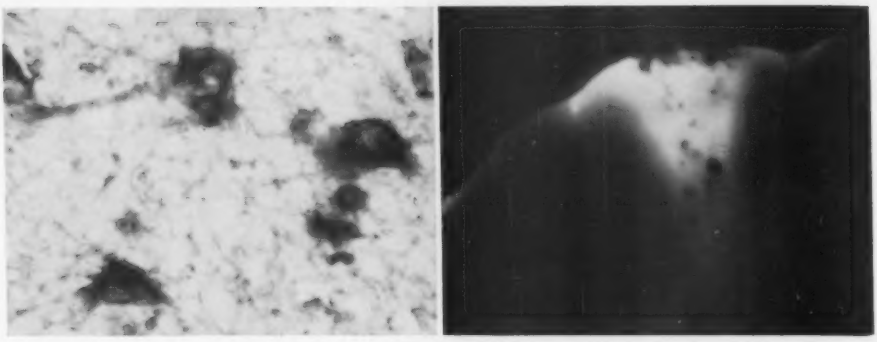

Fig. 5. *(Left)* Normothermic cat twenty-four hours after cold injury. An area from the edematous white matter underlying the cortical lesion. Intense PAS-positive staining of the swollen astrocytic cytoplasm. PAS stain. × 900

Fig. 6. *(Right)* Normothermic cat twenty-four hours after cold injury. Area of fluorescence extending through the white matter toward the base of the gyrus

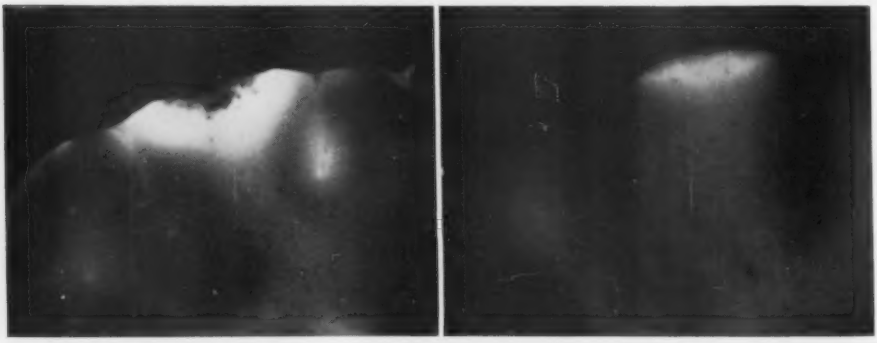

Fig. 7. *(Left)* Hypothermic cat of group II twenty-four hours after cold injury. Area of fluorescence is definitely smaller in comparison with Figure 6.

Fig. 8. *(Right)* Hypothermic cat of group III. Animal sacrificed after forty-two hours in hypothermia. The saucer-shaped area of fluorescence is limited to the cortex.

cytic cytoplasm and expansions (Fig. 5). The histochemical analysis indicated the glycoprotein nature of the PAS-positive substances in astrocytes. Cajal's gold chloride stain revealed the astrocytes to be markedly enlarged and frequently stretched in an axis perpendicular to the course of the nerve fibers and a majority of blood vessels (Fig. 10). Oligodendroglia showed no recognizable changes, and acute swelling of these cells was never observed. Similarly lacking was the microglial response. Study of the blood-brain barrier revealed a cone-shaped area of fluorescence extending through the white matter toward the base of the gyrus (Fig. 6).

Group II hypothermic animals sacrificed at twenty-four hours showed distinct differences with the corresponding normothermic group. The histologic evidence of edema in the white matter of the underlying cortical lesion gyrus

was markedly less pronounced. The astrocytes, stained with gold chloride, were conspicuously less swollen and distended (Fig. 11). Their cytoplasm stained PAS-positive; however, the area of PAS-positive staining of astrocytes in the white matter was definitely smaller than in the normothermic group. Observations under ultraviolet light revealed a wedge-shaped area of fluorescence reaching the white matter only immediately underlying the cortex and extending definitely less deep than in the corresponding normothermic cats (Fig. 7).

At forty-eight hours, the normothermic animals showed a slight reduction in the gross and histologic appearance of edema in the white matter of the corresponding gyrus. Astrocytes stained with Cajal's gold chloride remained markedly enlarged. Also, PAS-positive staining of this area remained almost the same. The fluorescent area showed slight reduction in size compared with the twenty-four-hour animals.

The forty-eight-hour group II hypothermic animals showed a definite increase in extent of fluorescence, astrocytic enlargement (Fig. 12), and PAS-positive staining in comparison with the twenty-four-hour hypothermic cats. However, these features did not attain the degree of intensity observed in the twenty-four-hour or forty-eight-hour normothermic animals.

At seventy-two hours, the fading of fluorescence was apparent in both groups I and II but was somewhat more noticeable in the hypothermic animals. Similarly, the PAS-positive staining, though still conspicuous, was greatly diminished in intensity in both groups, with the hypothermic animals showing less staining than their normothermic counterparts. The reactive astrocytes appeared to be of the same size in both groups.

At seven days, normothermic and hypothermic animals showed no differences in the permeability of the blood-brain barrier or in appearance of the astrocytes. In both groups, the area of fluorescence was limited to the cortex. Histologic evidence of edema was absent. The astrocytes, however, appeared markedly hypertrophic with conspicuous fibrous processes. The PAS-positive staining was confined to the walls of the blood vessels, as in the normal white matter of other gyri. No animals were sacrificed beyond seven days in group II.

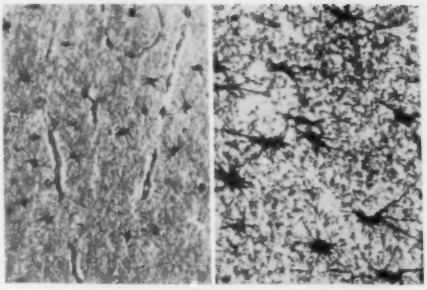

Fig. 9. *(Left)* Normal cat. Astrocytes in the white matter of the medial suprasylvian gyrus. Cajal's gold chloride stain. × 300 (For comparison to Figs. 10–12)

Fig. 10. *(Right)* Normormothermic animal twenty-four hours after cold injury. Marked enlargement of the astrocytes in the edematous white matter. Cajal's gold chloride stain. × 300

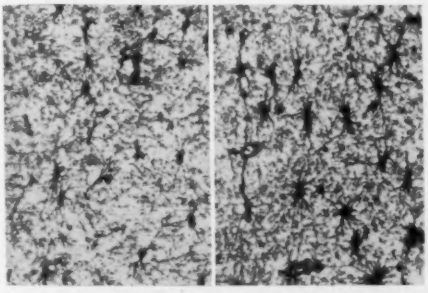

Fig. 11. *(Left)* Hypothermic animal of group II twenty-four hours after cold injury. Astrocytes markedly smaller than in Figure 10. Cajal's gold chloride stain. × 300

Fig. 12. *(Right)* Hypothermic animal of group II forty-eight hours after cold injury. Astrocytes appear larger than in Figure 11 but smaller than in Figure 10. Cajal's gold chloride stain. × 300

In group III animals, in which prolonged hypothermia was induced six hours after the application of the lesion and extended for forty-two hours, the observations concerning the blood-brain barrier and astrocytes revealed a picture strikingly similar to that seen in normothermic animals sacrificed six hours after cold injury. There was a marked widening of

the white matter of the gyrus underlying the cortical lesion. The area of fluorescence extended from the surface of the cortex to the border of the white matter, which remained nonfluorescent (Fig. 8). In the white matter of the gyrus, there was a PAS-positive staining of the astrocytes. In gold chloride stain, the astrocytes appeared enlarged and their distention corresponded in degree to that observed in the normothermic animals sacrificed six hours after application of the cold plate. Both PAS-positive staining and enlargement of astrocytes demonstrated by Cajal's gold chloride method were definitely less pronounced in this group than in animals of groups I and II at the forty-eight-hour stage.

DISCUSSION

The observations derived from this study provide a support for an assumption of a beneficial effect of hypothermia on cerebral edema. This assertion has been based primarily on an evaluation of the behavior of the blood-brain barrier and astrocytic reaction, which have been found previously to constitute a sensitive indicator in alterations of vascular permeability leading to edema. According to our studies,[5] the enlargement and PAS-positive staining of astrocytes appeared in the white matter within a few hours after application of the cold plate to the cortex and coincided closely with the development of edema. The appearance of green fluorescence in this edematous white matter, which signifies the breakdown of the blood-brain barrier for sodium fluorescein, was delayed for approximately eighteen hours; from then on, however, it paralleled closely the intensity of edema.

A comparative study of our standard cold lesion, with particular attention to the behavior of the blood-brain barrier and changes in astrocytes, revealed significant differences between hypothermic and normothermic animals. After twenty-four hours, the animals subjected to six hours of hypothermia showed a smaller area of fluorescence, less pronounced PAS-positive staining, and less intense astrocytic response than did the corresponding normothermic animals. It seems of interest that the peak of these changes related to edema was delayed in hypothermic (group II) animals and was reached at forty-eight hours, whereas the normothermic animals showed maximal edema at the twenty-four-hour stage. In certain analogy, according to our experience in patients who underwent intracranial surgery under hypothermia, the development of edema appears to be comparably delayed.

It is worth emphasizing that the maximal changes related to edema in hypothermic animals were always substantially less pronounced than those manifested in the normothermic group; this fact remains in accordance with the general clinical impression of a measure of benefit provided by reduction of edema after the use of hypothermia in intracranial procedures.

With regard to the effect of hypothermia on the development of the final astrocytic gliosis as a sequence of preceding edema, the observations from this study remain inconclusive. At seven days after application of the cold plate, the astrocytes were markedly hypertrophic in both normothermic and hypothermic (group II) animals. It is possible that the duration of edema was too short to demonstrate clearly the difference, or it might be that, even though reduced by hypothermia, alterations in permeability of the blood-brain barrier were still sufficient to result in the astrocytic gliosis of intensity that was observed in the normothermic group.

The induction of hypothermia in animals of group III six hours after application of the lesion and continued for forty-eight hours was intended to serve for assessment of the value of hypothermia in brain injury when applied after the delay of several hours. Our experimental schedule was designed to parallel a likely clinical situation in which several hours may elapse after brain injury until the hypothermia can be induced. Rosomoff[1] demonstrated that in dogs the protection against infarction offered by hypothermia is feasible only if initiated within fifteen minutes after the occlusion and if the temperature of 24° C. was reached within a total elapsed time of ninety minutes. The duration of hypothermia in his experiments did not exceed one hour. In the present study, the intention was to assess the effect of a prolonged hypothermia (forty-two hours), especially in view of the fact that the maximal edema in our experiments was established only after twenty-four hours in normo-

thermic and after forty-eight hours in hypothermic (group II) animals. Unfortunately, after forty-two-hour hypothermia at 26° C., we were unsuccessful in consistently keeping the animals alive after rewarming. Nevertheless, the animals sacrificed after this prolonged hypothermia provided some interesting observations. The degree of edema as well as changes in the permeability of the blood-brain barrier and in astrocytes closely resembled a picture that resulted after six hours without hypothermia, that is, corresponded to the time when hypothermia was initiated. It would almost appear that the edema became "stabilized" in the state that was present at the time of induction of hypothermia, that is, it showed no significant progression throughout the duration of the lowered body temperature. If this assumption is true, attention should be focused on the period following the termination of hypothermia, since it is at that time that the final outcome of edema is possibly determined. In particular, it would appear that the problem of gradual rewarming should deserve further investigation in view of its important clinical implications.

SUMMARY

1. A comparative study between normothermic and hypothermic animals was undertaken using an experimental cold injury associated with an area of edema in the white matter of the gyrus underlying the cortical lesion.

2. Significant differences were noted between normothermic and hypothermic groups of animals in the degree of edema, permeability of the blood-brain barrier, and behavior of the astrocytes.

3. After twenty-four hours, animals with lesions produced under hypothermia continued for six hours showed a markedly smaller area of fluorescence and less pronounced enlargement and PAS-positive staining of astrocytes than their normothermic counterparts.

4. In the hypothermic group II, the peak of edema was delayed and appeared at forty-eight hours, whereas in the normothermic animals it was reached at the twenty-four-hour stage. The peak in the degree of edema in the hypothermic animals was definitely less pronounced than the maximal intensity of edema in the normothermic group.

5. After one week, the areas of fluorescence and astrocytic response were almost indistinguishable in both groups.

6. Group III animals, in which hypothermia was initiated six hours after the lesion was produced and was maintained at 26° C. for forty-two hours, showed a degree of edema resembling the stage after six hours in normothermic animals, that is, the stage when hypothermia was initiated.

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Monozygotic twins concordant for Huntington's chorea

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THE PURPOSE of this report is to present what is believed to be the first case of monozygotic twins concordant for Huntington's chorea in whom monozygosity has been adequately documented and to describe and discuss the occurrence of Huntington's chorea and mental illness in the family of the twins, with emphasis on some clinical, pathologic, and genetic features.

Since Huntington's famous description of "hereditary chorea" in 1872, about 20 cases of chorea in twins have been reported; 8 of these were allegedly in identical twins, although in no case was the identity of the twins adequately documented. The literature up to 1935 has been summarized by Bell,[1] but no effort was made to pick out twin cases.

Russell[2] in 1894 described the case of male twins who had chorea with equivocal signs of mental deterioration at age 27, a little earlier in one of the twins. Their identity was based on their remarkable likeness in appearance. Another family in which there were male twins discordant for Huntington's chorea was reported by Rosenthal[3] in 1927. The affected twin had symptoms at age 29, although chorea was not diagnosed until ten years later. At age 40, his co-twin was not affected. No evidence of zygosity was presented. Popenope and Brousseau,[4] in 1930, published a brief report in which they merely stated that they observed identical twin males, age 60, both affected with Huntington's chorea. Rosanoff and Handy[5] in 1935 reported the case of female monozygotic twins affected with Huntington's chorea in whom symptoms appeared at age 35. The twins are described as being so similar in features and build that "they could not be told apart and their records became very much mixed." In an extensive article in which he also reviewed the literature up to 1940, Entres[6] reported 2 twin cases from his own observations. The first were female twins whom the author regarded as "definitely monozygotic." They both became affected at age 41 and died at ages 54 and 56. The second pair was of male, "presumably" monozygotic twins who both showed choreic symptoms at age 45 and died at ages 64 and 65. No evidence of monozygosity was presented even for the "definitely" monozygotic pair. Jelgersma[7] in 1957 reported the case of twin sisters concordant for Huntington's chorea. The one twin, 57 years old, was choreic since age 45 and mentally deteriorated. Her twin sister was affected with Huntington's chorea and died of an apoplectiform attack at age 54. Apparently, the deceased twin was never seen by the author, but he expressed the opinion that there were strong indications that the twins were identical on the basis of their striking resemblance and mutual love. Parker[8] in 1958 described the occurrence of Huntington's chorea in male twins "who were identical in appearance." In both, involuntary movements commenced at the age of 42 years, and the twins died within three months of each other.

We are presenting here 3 cases of Huntington's chorea in two generations of the G family (Fig. 1). The propositae are identical twin sisters, both suffering from Huntington's chorea. Their father was likewise affected. A sister of the twins has schizophrenia.

This family stems from Germany. The grandparents, I-1 and I-2, and their 5 children

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were born in Germany and then emigrated to the United States, with the exception of the grandfather, described as a "drunken band leader," who died in his sixties and may have been choreic. The grandmother died of a heart attack when she was 52 years of age, without symptoms of chorea.

Of the 5 children, only II-10, the father of the twins, had Huntington's chorea, though all lived into middle age and some into old age. III-21 is said to have had Sydenham's chorea in childhood.

The father, II-10, born in 1887, received a college degree and worked as an engineer. There is no reliable history as to when he began having involuntary movements. At age 54, he was hospitalized because of "a chronic motor disorder." The diagnoses made at the time were hysteria, Huntington's chorea, and osteitis deformans. He was discharged two years later but returned soon because of deterioration. At age 57, he was transferred to another hospital, where on admission he was described as quarrelsome, childish, and disoriented in time and as having poor memory, defective speech, and no insight into his condition. Neurologic examination revealed generalized choreoathetoid movements, rigidity of the neck, generalized spasticity, positive Kernig's sign bilaterally but normal deep tendon reflexes, and flexor plantar responses. Laboratory data were within normal limits except for leukocytosis of 16,000 and blood sugar of 133 mg. per 100 cc. Roentgenographic examination of the skull and long bones revealed Paget's disease.

The diagnoses made were Huntington's chorea with mental deterioration "in spite of absence of similar condition in the family history" and osteitis deformans. He continued to lose weight and had decubitus ulcers. Terminally, he showed symptoms of "impaired cir-

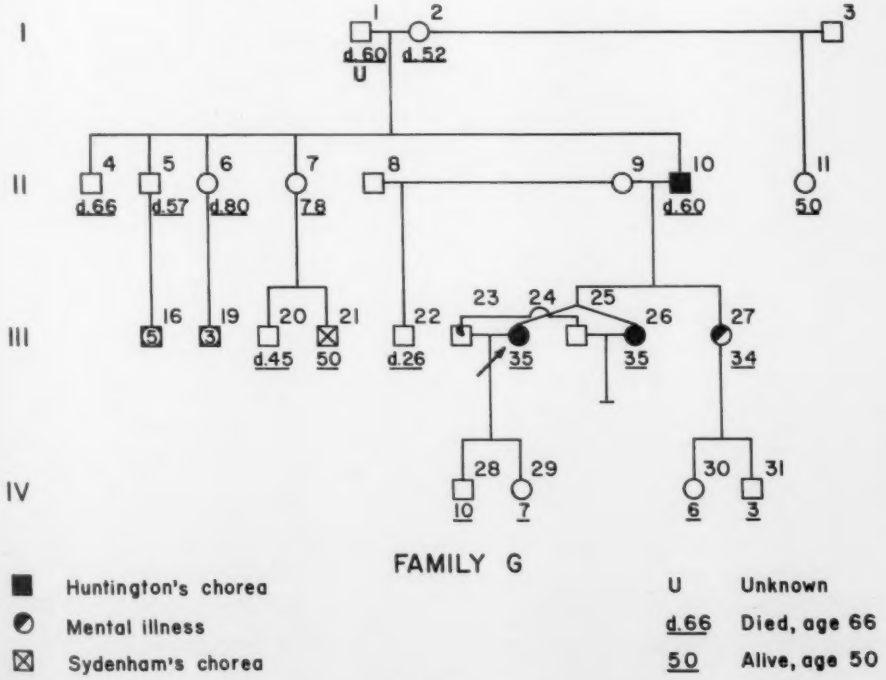

Figure 1

culation and cyanosis" and died on August 24, 1947, at age 60.

At autopsy, acute bronchopneumonia and osteitis deformans were noted. The brain showed a reduction in the width of the gyri, especially of the frontal lobes in their middle portion and in the upper portion of the parietal lobes close to the sagittal fissure and, to a lesser extent, over the frontal lobes. Microscopically, there was a striking atrophy of the cortex in many sections with definite evidence of gliosis and fairly numerous corpora amylacea. In the corpus striatum, the large ganglion cells and small and large neurons showed extensive changes in the form of atrophy and chromatolysis. Neuronophagia was observed in many areas, and there appeared to be an overabundance of cerebral histiocytes in the areas of large cell atrophy. Small, scattered foci of sponginess occurred in the basal ganglia in both the neostriatum and paleostriatum. Siderosis of many medium and small intracerebral arteries was observed, with extensive hyalinization and thickening of the walls. Surrounding these arteries were foci of gliosis with numerous corpora amylacea. The pathologist regarded these lesions as a degenerative process involving the cortex of the brain as well as the central nuclei. He expressed the opinion that the lesions were consistent with but not specific for Huntington's chorea.

The case was subsequently reviewed by another pathologist who found the evidence insufficient to support the diagnosis of Huntington's chorea and considered the case one of cerebral arteriosclerosis.

The twins, E. M., III-24, and P. M., III-26, were born in 1923 with 1 placenta, according to their mother who was a nurse. They grew up together, graduated from nursing school, served together in the Army Nursing Corps for one year, and married 2 brothers.

E. M., III-24, at age 22 was noticed by others to display a certain clumsiness of voluntary movements. About a year later, shortly after her marriage, the patient noticed that she dropped dishes and other objects easily. At about age 27, her housekeeping habits became less meticulous and her interest in outside activities waned. Her handwriting became less legible, and she began not only to speak indistinctly but also to curse when not understood. Her memory began failing, and she had difficulty with calculations. At age 28, her husband noted spontaneous kicking in bed. By that time, she had had two children, and, during her third pregnancy, at age 29, the diagnosis of Huntington's chorea was made. Abortion and tubal ligation were performed during the third month of pregnancy. At the age of 32, her involuntary movements had so progressed that driving an automobile became impossible and, despite an increased food intake, she lost considerable weight, totaling 30 lb. to date. Reserpine, 4 mg. daily, produced a decrease in movements and an increase in weight but only transiently. For the past year, she has been unable to do any housekeeping. Five months ago, her movements suddenly became much worse and so fatiguing that she has since been virtually confined to bed.

Physical examination on June 9, 1958, at the National Institutes of Health revealed a young white female with evidence of marked weight loss and in constant agitation. Mild pectus excavatum was noted. Involuntary movements of sudden onset and sudden termination, asymmetric and nonrhythmic, affected all the somatic muscles. When supine, she had quiet movements, but violent trunk movements attended her sitting up. Walking without aid was to risk falling, and attempts to feed herself caused spillage. She was unable to fasten buttons or to write her name legibly. The deep tendon reflexes were symmetrically hyperactive without clonus, and the plantar responses were extensor bilaterally. Muscle tone was not altered, and no localized atrophy was noted. Joint position sense and possibly other secondary modalities were impaired in the extremities. Her speech was perseverative and very poorly articulated, permitting only monosyllables. She was oriented except for the date. She was unable to recall an address after three minutes, to carry out multiple commands, or to perform serial 7 subtraction. Urinalysis and complete blood count were normal. Serum copper was 154 and 171 μg. per cent on 2 determinations. Her electroencephalogram was diffusely abnormal with predominance of fast activity superimposed on poorly developed, irregular, slow activity. No focal abnormalities or epileptiform discharges

ONSET, PROGRESS, AND PRESENT STATUS OF HUNTINGTON'S CHOREA IN THE TWINS E.M. AND P.M.

	E.M., III-24	*P.M., III-26*
1. *Chorea*		
Clumsiness	22 years	22 years
Involuntary movements at rest	28 years	29 years
2. *Dementia*		
Careless housekeeping Speech and writing difficulties Impairment of memory Altered disposition	27 years	33 years
3. *Present status*		
Involuntary movements	violent	moderately severe
Emaciation	severe	mild
Mental deterioration	severe	mild

were found. Psychologic testing with the Rorschach test showed a typical picture of severe organic deterioration.

P. M., III-26, strikingly resembled her twin in the development of her illness. At age 22, her voluntary movements were noted to be awkward. At the age of 26, she began falling and became argumentative. At age 29, her husband noticed spontaneous kicking in bed. At age 33, her speech and handwriting became less legible. As her movements became more severe, her weight also decreased. She, too, received transient benefit from Reserpine but became suddenly worse five months ago. At present, she, like her sister, is virtually confined to bed.

Physical examination on June 9, 1958, at the National Institutes of Health revealed a well-developed, young white female who appeared adequately nourished. Pectus excavatum was marked. Her involuntary movements were similar to those of her twin sister, though less severe, permitting her to walk without assistance. The deep tendon reflexes were symmetrically hyperactive, and there was unsustained clonus in the lower extremities. The plantar responses were extensor, the muscle tone normal, and the position sense unimpaired. Speech and mental state were similar in nature to those of her twin sister, although she showed less memory impairment for recent events.

Urinalysis was negative except for 1 + glucose on 2 occasions. White blood count was normal. Serum copper was 105 and 106 μg. per cent on 2 determinations. Her electroencephalogram was abnormal, showing a mild degree of diffuse dysrhythmia of cortical or subcortical origin. Psychologic testing with the Rorschach test showed milder organic deterioration than that of her twin sister.

An over-all picture of the onset and progress of the disease in the twins is given in the table.

The zygosity of the twins was determined by comparison of physical characteristics, fingerprints, and blood groups. A probability figure in favor of monozygosity was then calculated with the objective method described by Smith and Penrose.[9]

The twins were very dissimilar with respect to general appearance (Fig. 2) and weight. This is not surprising since the one twin has had movements of a severe character for a longer period than the other, resulting in more emaciation, facial contortion, and general disfigurement. The twins were concordant, however, with respect to the following: Huntington's chorea; sex; appearance before onset of chorea (Fig. 2); pectus excavatum; eye color; pigmentation pattern of the iris; hair color, texture, and form; skin color; ear lobe configuration; and the following blood groups: A_1, M, U, P, cc D Ee, k, Fy^a+, Jk^a+, He–.

The total finger ridge count for E.M. was 138 and for P.M., 148, a difference of 10.

The probability in favor of monozygosity calculated with the objective Smith-Penrose

Fig. 2. (*Left*) The twins before the onset of chorea. (*Right*) The twins at the time of examination, approximately seven years after the onset of involuntary movements

method was 0.9781. It is felt that, for practical purposes, the identity of the twins has been demonstrated.

M.R., III-27, the younger sister of the twins by one year, is not known to be choreic but illustrates a point made in the discussion. During most of her adult life, she has had a certain clumsiness of her hands and could not learn to type or take shorthand well. At the age of 23, she suffered a psychotic episode "which had all the earmarks of an incipient schizophrenia," for which she received 5 shock treatments. In 1946, when her father had been hospitalized for five years, M.R. asked for marriage counseling for herself and her sisters from a physician who was very well acquainted with her father's case. She was advised that the possibility of inheriting Huntington's chorea was very small and that it would not play a part in their marriage plans. She therefore married, as did her sisters, and had 2 children. At age 29, neurologic examination showed slight slurring of speech and emotional instability. In the past three years, appalled at the mental and physical deterioration of her sisters, she has had delusions that she also was afflicted, despite the inconclusive evidence, has attempted suicide, and has required hospitalization and electroshock treatments. The present diagnosis in her case is schizophrenia. Examination by one of us (P.R.) in January 1959 disclosed slow speech, not clearly articulated. Neurologic examination was otherwise within normal limits. Coordination was satisfactory, and she manifested no chorea despite her delusion to the contrary. Her mood was mildly depressed, her affect flat, and her judgment beclouded by unrealistic fears. In her present emotional state, evaluation of her intellectual capacities is not satisfactory.

DISCUSSION

Huntington's chorea is a hereditary disease characterized by the appearance in adult life of progressive chorea and dementia and inherited in single autosomal dominant fashion. The cases in the family described in this report demonstrate these features.

The neuropathologic features noted here and in many previous cases described in the literature are generally regarded as lacking specificity.[10–13]

McMenemy,[13] in his recent review, states that the symptomatology of Huntington's chorea does not always correspond with the pathologic findings, a feature that complicates the study of this disease.

In Huntington's chorea, at present, the clinical findings and family history are of more diagnostic value than the pathologic findings. Consequently, the interpretations given of the pathologic findings in the case of II-10 are necessarily arbitrary.

There can be little doubt but that schizophrenia in the case of III-27, M.R., was partly precipitated from knowledge and fear that she was a potential heir to a dementing, disabling disease. It is interesting to note, however, that, at the time of her first psychotic episode, her physician thought that her psychosis might be the first manifestation of Huntington's chorea. Tusques and Feuillet,[14] Laane,[15] and others have described schizophrenia and other psychotic reactions preceding the onset of choreic symptoms by many years. Evard[16] considers the occurrence of schizophrenia in choreic families as "phenotypic polymorphism" of Huntington's chorea. It is possible, therefore, that the psychotic episodes in the case of M.R. are prodromal manifestations of chorea and that she may later develop the disease.

M.R. sought genetic advice for herself and her sisters seventy-four years after Huntington's description of the disease, commonly used among the medical profession to exemplify dominant inheritance with complete penetrance. A physician aware of her father's diagnosis gave her the wrong advice, and tragedy ensued. Since genetic counseling centers are few and not always available to the general public, the practicing physician is the person most likely to be consulted in these circumstances and has a grave responsibility to provide accurate genetic information to those who seek it. In turn, the responsibility for giving the physician adequate background in genetics rests with our medical schools, hospitals, and other training institutions.

SUMMARY

1. The occurrence of Huntington's chorea in female monozygotic twins and their father is described.

2. Some aspects of the pathology of Huntington's chorea, the relation of schizophrenia to the disease, and genetic counseling with reference to this family are briefly discussed.

A bibliography of Huntington's chorea, 1934-1959, with additional reference on twins since 1889, can be obtained from Dr. Myrianthopoulos or from the library of the National Institutes of Health.

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Low spinal fluid pressure syndromes

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Adolph L. Sahs, M.D.

THE MECHANISMS of production and the factors participating in the control of cerebrospinal fluid dynamics have been the source of many intriguing studies. That cerebrospinal fluid issues from the choroid plexus was suggested by Cushing,[1] who observed the appearance of drops of fluid on the surface of the choroid plexus during surgery. Dandy[2] provided further evidence when he occluded the outlet of one lateral ventricle and produced a unilateral ventricular dilation.

Such observations, however, were not universally accepted, and other sources of cerebrospinal fluid were described.[3,4] The accumulated evidence from numerous experimental and clinical studies on the problem has now given most support to the theory that the choroid plexus certainly represents the most important site of fluid formation. After formation, many and varied factors are responsible for maintaining an equilibrium, so that the relationships of the intracranial contents in their rigid skeletal container remain relatively constant. With certain disturbances of these regulating mechanisms, clinical syndromes of cerebrospinal fluid hypertension or hypotension appear. Those entities associated with intracranial hypotension are the subject of this report. It has long been known that clinical symptoms could result from alterations in intracranial pressure. Hoseman,[5] in 1909, provided one of the original reports on headache from cerebrospinal fluid hypotension after spinal anesthesia. Thereafter, many reports concerning the various forms of intracranial hypotension and its management appeared in the foreign literature.

A classification of low spinal fluid pressure syndromes might be listed as follows: [1] spontaneous or primary, [2] postoperative (cranial), [3] after head trauma, either with or without manifest external loss of cerebrospinal fluid, [4] after lumbar puncture or nerve sleeve tears, and [5] secondary to other medical conditions, such as dehydration, or instances of decreased cerebral blood flow as in cerebral arteriosclerosis.

Spontaneously occurring intracranial hypotension develops without an obvious precipitating event in contradistinction to the last 4 types. Schaltenbrand[6] introduced the syndrome of spontaneous intracranial hypotension in 1938 and referred to it as aliquorrhea. On cursory examination of such a patient, the examiner is often erroneously led to suspect an encephalitic process of infectious etiology or a syndrome associated with increased intracranial pressure. The diagnostic value of a carefully executed lumbar puncture in this situation cannot be overemphasized, since demonstration of low or absent cerebrospinal fluid pressure in the lateral recumbent position clarifies the issue. The following 5 cases represent low spinal fluid pressure syndrome; 3 are reported as examples of the spontaneous type, while the other 2 patients had their illnesses after slight trauma in the form of falls on the buttocks. Of special interest was the occurrence in 1 patient of intracranial air appearing on roentgenograms, apparently resulting from diagnostic lumbar puncture. As will be described later, it is felt that the reduction in intracranial pressure in this patient resulted in spontaneous aspiration of air through the lumbar puncture needle and into the subarachnoid space when the diagnostic procedure was performed.

CASE REPORTS

Case 1. This 29-year-old woman was admitted to University Hospitals on June 21, 1956, because

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of headaches. Eight days before admission, she fell on her buttocks while playing basketball. She had back pain the next day and, in two days, had severe bitemporal headaches, dizziness, and blurred vision only when upright. She was hospitalized locally, and lumbar puncture was performed. There were 2 cells present, but the pressure findings apparently were not recorded.

On transfer to University Hospitals, the general physical and neurologic examination was normal. She was afebrile, and routine laboratory studies were normal. The initial lumbar puncture was unusual in that the pressure in the lateral recumbent position was not obtainable and rose to only 160 mm. of water when she was placed in a sitting position. Free rise and fall were noted on coughing but not on jugular compression. The fluid was xanthochromic with 978 cells, mostly lymphocytes. Protein value was 81 mg. per cent and sugar value, 42 mg. per cent; cultures were negative. She was started on antibiotics, and the spinal fluid examination was repeated six days later. Again, a pressure determination was not obtainable in the lateral recumbent position. Sitting pressure was 190 mm. of water, and there was no rise or fall on jugular compression; 12 cells were found, and the protein value was now 100 mg. per cent. Antibiotics were discontinued, and she was maintained on bed rest with her feet elevated.

She did not improve, however, so another lumbar puncture was performed twenty-one days after admission. Again, the pressure was not obtainable; the aspirated fluid had 36 cells and a protein determination of 48 mg. per cent. Because of the initial high protein content and no reaction to jugular compression, a cervical myelogram was performed thirty-three days after admission. The cerebrospinal fluid pressure again was not obtainable. However, the fact that the needle was in the subarachnoid space was demonstrated by the injected dye flowing freely to the cervical region without evidence of block or deformity. Two days thereafter, another lumbar puncture showed a normal pressure, with prompt rise and fall on jugular compression, a protein content of 70 mg. per cent, and 4 cells. A pneumoencephalogram performed one week later was normal. She was discharged and, on reexamination in the outpatient clinic one and four months later, still had slight headaches but was otherwise well.

Case 2. This 13-year-old girl was admitted to University Hospitals on October 7, 1957, with severe headache and back pain radiating into the posterior portion of the right thigh. The patient was well until three days before admission, when she fell on her buttocks. She had severe pain that radiated down the right leg and was made worse by coughing. Two days later, she noted severe headache that was relieved by lying down and aggravated in the upright position.

Her general physical and neurologic examination was entirely normal except for pain in the right thigh when she bent forward. In the hospital, she had no headache when supine but would promptly have a headache when she was placed in the upright position. Her laboratory studies were normal. A lumbar puncture was performed. The initial pressure was 40 mm. of water, with a free rise and fall on jugular compression and release. Protein value was 42 mg. per cent. She improved in the hospital on bed rest and was discharged four days later with no symptoms.

Case 3. This 45-year-old woman was admitted to University Hospitals on September 4, 1957, because of nausea and vomiting, headache, and staggering gait for one week. The day before admission, her memory became disturbed and, although her headache was less intense, her neck became stiff. Generalized weakness was also a notable symptom on admission.

Approximately seventeen months before admission, the patient's left kidney was removed for tuberculosis. No further known complications had appeared from this episode. Physical examination on admission revealed a blood pressure of 80/60 mm. Hg. She appeared quite ill, with sunken eyes and sallow skin but was afebrile. The patient was lethargic but could be aroused and was able to give a fairly reliable history. Mild neck stiffness was demonstrated. No other abnormal findings were elicited on examination.

Lumbar puncture was done shortly after admission, but, although the needle was felt to penetrate the dura, no flow of fluid occurred. After several attempts, a syringe was attached to the needle and, with gentle aspiration, spinal fluid appeared. The opening pressure was thus recorded as less than 30 mm. of water. There were 250 fresh red blood cells per cubic millimeter, believed to be traumatic. Protein value was 32 mg. per cent; glucose and chloride values were normal. Smear and culture of the fluid were negative.

With bed rest, she soon began to improve and was discharged four days after admission. She returned on September 24, three weeks after admission. She had continued to improve and had had some nausea and only occasional headaches since discharge. However, six days after discharge, she noticed double vision that persisted until her return. On examination, she was found to have left abducens paresis to account for the diplopia. Otherwise, her physical status had markedly improved as compared with the initial findings.

Case 4. This 44-year-old woman was admitted to University Hospitals on October 30, 1956, because of headaches for three months. The pain was occipital in location and had become gradually more frequent and more severe until one week before admission, when it became continuous. The headache was definitely made worse by sitting or standing. In addition, the upright position also was associated with vertigo and vomiting.

Fig. 1. *(Case 5)* Plain skull roentgenogram, posteroanterior view. Note air in the ventricular system which appeared after diagnostic lumbar puncture.

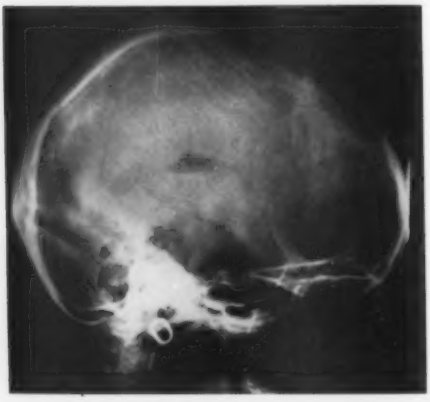

Fig. 2. *(Case 5)* Plain skull roentgenogram, lateral view, shows air in the upper part of the ventricular system.

Lumbar puncture had not been done before her entrance to University Hospitals.

Physical examination revealed an acutely ill patient who became pale, appeared faint, and vomited on sitting. Blood pressure was 100/60 mm. Hg, and pulse rate was 56 per minute and regular. The neck was mildly stiff, and pain resulted from forward flexion of the head on the neck. The remainder of the general physical and neurologic examination was normal.

Lumbar puncture on the day of admission revealed an opening pressure of 60 mm. of water, no cells, and protein of 98 mg. per cent. When lumbar puncture was repeated three days later, no pressure could be recorded in the lateral recumbent position. In the sitting position, the fluid rose to 340 mm. of water, well below the level of the foramen magnum. The protein determination was 62 mg. per cent. Three days later, a pneumoencephalogram revealed a normal ventricular system and subarachnoid space. Again, no cells were found in the fluid, and, as before, smear and culture were negative. Other studies included normal skull and chest roentgenograms. Complement-fixation tests for various encephalitides, heterophile agglutination, and serologic tests for syphilis all were negative.

Thereafter, she began to improve symptomatically and continued to do so until complete recovery was attained. When seen one year after her illness, she was without symptoms.

Case 5. This 22-year-old woman was admitted to University Hospitals on December 4, 1956. Her illness had begun nine days before admission with the sudden occurrence of throbbing occipital headache. Shortly thereafter, she noticed vertigo on bending forward, as well as weakness and faintness. The headache became worse, and vomiting occurred once before admission.

Physical examination on admission demonstrated an alert and cooperative but acutely uncomfortable woman. While the history was obtained, she was observed to keep her eyes closed and appeared more uncomfortable on opening them. Rapid changes of position, such as changing from a supine to a sitting position, made her become pale and feel faint. Neck stiffness was not demonstrated. The remainder of the examination was within normal limits.

Lumbar puncture was done the evening of admission and showed an opening pressure of 30 mm. of water. No cells were found in the fluid, and protein content was 44 mg. per cent. Glucose and chloride values were normal. The next morning, approximately twelve hours after lumbar puncture, roentgenograms of the skull were taken. These films showed a small quantity of air in the lateral ventricles (Figs. 1 and 2). Other studies included negative heterophile and viral complement-fixation tests. Two days after admission, she began to improve and continued to do so until complete recovery had occurred.

DISCUSSION

Spontaneous intracranial hypotension. Of the 5 cases reported above, the last 3 are believed to be examples of spontaneous intracranial hypotension. The first reference to this illness which we have been able to find was made by Schaltenbrand[6] in 1938; two years

later, the same author reported 3 cases[7] that he designated as "aliquorrhea." Schaltenbrand[7] pointed out the characteristic onset with headaches made worse in the upright position, nausea, vomiting, and generalized symptoms of weakness. All 3 patients made uneventful recoveries and were discharged without symptoms. Cases 1 and 3 were of particular interest in that, at the time lumbar puncture was done, a sucking sound was heard when the stylet was withdrawn from the needle, probably indicating aspiration of air through the needle and into the subarachnoid space. Roentgenograms of the skull after the procedure showed air in the ventricle in Case 1 and air in the subarachnoid space in Case 3. In our patients, a similar occurrence was noted in Case 5. Lumbar puncture showed an opening pressure of 30 mm. of water, and, as the stylet was removed, a sucking noise was very evident. Several hours later, skull roentgenograms revealed air in the uppermost aspect of the lateral ventricles. It must be assumed that, if the intracranial pressure becomes less than atmospheric pressure in the lateral recumbent position, air may be aspirated when a needle is placed into the subarachnoid space. Puech and associates[8] reported a case with spontaneous onset in which depressive symptoms and mental confusion were the predominant symptoms. On trephination, the brain was sunken away from the skull. However, no definite pressure measurements were obtained. This patient eventually expired, and, at autopsy, marked atrophy of the choroid plexus was found. It is highly questionable if such a case as this should be included in this group of illnesses. Hesser[9] added 2 instances of spontaneous intracranial hypotension. The first appeared in a 39-year-old man, and the second involved a 34-year-old woman. Headaches developed suddenly in the first case and gradually in the second; in both instances, however, the headaches presented a distinct orthostatic feature: very severe in the upright position but relieved when the patient was supine. In both, the opening pressure at lumbar puncture was zero. Both patients ultimately experienced complete recovery. In another patient described by Lindqvist and Moberg,[10] the clinical impression was meningitis. On lumbar puncture, the fluid rose in the manometer with the patient sitting. However, when he was placed in the lateral recumbent position, the fluid column fell until it disappeared and a sucking noise was then observed, as noted above. Although he was ill for approximately two months, this patient completely recovered. These authors favored the term "hypoliquorrhea," indicating the existence of at least some cerebrospinal fluid. Other instances of spontaneous spinal fluid hypotension have been reported.[11] The most recent review of the subject was that of Shenkin and Finneson[12] in 1958. The authors described 32 cases with low spinal fluid pressures, believed to be spontaneous in onset in 3.

Review of the literature of low spinal fluid pressure syndrome occurring spontaneously, plus the evaluation of our reported cases, indicates that one might expect a fairly consistent constellation of clinical findings in such a case. Headache, characterized by extreme aggravation in the upright position and relief on lying down, is almost always present. Onset of this symptom may be either sudden or gradual. Headache may, at times, become extremely severe, so that the patient will have nausea or vomiting, dizziness, or faintness when erect. On resuming the horizontal position, many such patients will obtain remarkable relief and often remain quite comfortable in bed. It is likely that the headache in this condition is the result of traction on the pain-sensitive intracranial structures, including the great vessels at the base of the brain, tributary veins to the sagittal sinus, and the venous sinuses, as suggested by Ray and Wolff.[13] Photophobia, anorexia, generalized malaise, dizziness, and vertigo may also be recorded in spontaneous intracranial hypotension. Minimal or mild stiffness of the neck is often found, together with pain induced by forward flexion of the head. Blood pressure is usually not altered. However, the pulse rate is often slow. Schaltenbrand[7] referred to the bradycardia in this condition as "vagus pulse." Alterations in the state of awareness and mental confusion have been described. However, they are not usually so prominent in spontaneous intracranial hypotension as in those hypotensive syndromes believed to be associated with a decreased cerebral blood flow, such as in the posttraumatic or postoperative type. Seizures have been

mentioned.[8,11] This complication must be considered an unusual manifestation of spontaneous intracranial hypotension. Rarely, psychiatric disturbances also have been prominent in certain cases with spinal fluid hypotension. Depression,[8] schizophrenic-like states,[11] and melancholia[8] have been described. Spontaneous intracranial hypotension may readily be confused with meningitis or encephalitis, subarachnoid hemorrhage, or an increased intracranial pressure syndrome. The absence of papilledema in intracranial hypotension helps differentiate it from states of increased pressure.

Careful lumbar puncture is a necessity for accurate diagnosis of this syndrome. Pressure determination in the lateral recumbent position will usually reveal the opening pressure to be 30 or 40 mm. of water, if it is measurable at all. Should the examiner feel the needle penetrate the dura and enter the subarachnoid space, it is imperative that he apply gentle aspiration with a small syringe if no fluid appears. If the spinal fluid pressure is the same as atmospheric pressure or lower, no fluid may be obtained until it is aspirated. In these cases with very low pressure, a sucking noise may occur when the stylet is removed from the needle after the subarachnoid space has been penetrated. If a pressure reading cannot be obtained in the lying position despite the fact that the examiner feels the needle tip is in the subarachnoid space, the patient should be placed in the sitting position. Usually, the fluid will now be seen to rise in the manometer. In intracranial hypotension, however, the fluid column will not reach the level of the foramen magnum, as in normal persons. In addition to the low spinal fluid pressure, jugular compression in these patients results in a sluggish rise or no response. It is common to find red blood cells in the spinal fluid of patients with spontaneous intracranial hypotension, although the mechanism is not clear. Our Case 3 had 250 erythrocytes per cubic millimeter; all 3 of Schaltenbrand's[7] original cases showed numerous red blood cells, and Hesser's[9] Case 2 had 19,000 erythrocytes per cubic millimeter. Schaltenbrand[7] postulated that, with cessation of fluid secretion at the choroid plexus, hyperemia of the brain and meninges occurs and there is diapedesis of red cells. Hesser[9] has suggested that some of the bleeding into the subarachnoid space in these cases might be due to alteration of relative pressures in the subarachnoid space, particularly with respect to the veins lying therein. Normally, the intrathecal pressure about equals the venous pressure. With spinal fluid hypotension, a different situation tends to occur. The spinal subarachnoid space now becomes reduced in depth because of the decreased fluid pressure and thus becomes much more vulnerable to repeated punctures by the operator vainly trying to obtain cerebrospinal fluid. That this explanation does not account for all the red blood cells found in the spinal fluid in these cases is evidenced by the fact that xanthochromia is sometimes found on the initial lumbar puncture and under circumstances that are judged to be nontraumatic. A white cell response, as seen in our Case 1, has not been reported commonly. Schaltenbrand's[7] Case 3 showed leukocytic pleocytosis. In addition to the cellular findings and xanthochromia, mild to moderate spinal fluid protein elevation may be found in spontaneous intracranial hypotension. As mentioned, accurate lumbar puncture is the most valuable diagnostic method in this illness. Puech, Perrin, and Koechlin[14] advised against lumbar puncture in suspected cases of intracranial hypotension because of the danger of ventricular collapse. The latter authors felt that trephination with visualization of the brain retracted away from the skull permitted a diagnosis with less risk. It is unlikely, however, that lumbar puncture will lead to serious complications in intracranial hypotension if done cautiously. The only complication we observed, transient left abducens paresis, occurred in Case 3. Abducens paralysis after lumbar puncture has been reported previously.[15,16] Indeed, Quincke[17] described a transient bilateral abducens paralysis after removal of a considerable quantity of fluid from one of the first patients on whom the procedure of lumbar puncture was done.

The pathogenesis of spontaneous intracranial hypotension remains unclear, although numerous suggestions have been proposed. That the choroid plexus is innervated by a dense nervous plexus is well known, but the neural and humoral factors that control plexus function and cerebrospinal fluid secretion are not

yet fully defined. The surface of the choroid plexus has been shown to be covered with villous fronds, each of which is composed of numerous villi containing a capillary network and a surface epithelial layer. A direct arteriovenous communication exists in each frond and provides a potential means for reducing the plexus blood supply.[18] The controlling factor for function or nonfunction of this mechanism is not clear. Schaltenbrand[19] postulated that spontaneous decrease or cessation of spinal fluid production was the result of a reversible disturbance of vasomotor function of the choroid plexus. It is conceivable that an irritable vasomotor mechanism might exist in some individuals and might produce spasm of the choroid plexus vessels. Toxic factors or infection might result in a similar phenomenon. Certainly, the high leukocyte count in the spinal fluid in Case 1 of our series is compatible with an infectious process. The possible existence of hypothalamic control of spinal fluid formation[11,14,20,21] is of interest. Its importance in the pathogenesis of spontaneous intracranial hypotension remains to be seen. A single case of hypopituitarism and intracranial hypotension was reported by Homann.[22] However, the entire clinical picture appeared after repeated irradiation to the region of the choroid plexus for the treatment of communicating hydrocephalus. It is likely that decreased spinal fluid formation in this case resulted from irradiation effects on the choroid plexus.

Postoperative intracranial hypotension. Intracranial hypotension has been noted[23,24] after a variety of neurosurgical procedures but appears most often in association with evacuation of subdural hematoma or after procedures directed to the posterior fossa. This complication may be suspected in a patient who continues to be drowsy and apathetic postoperatively and who does not become responsive as expected. The presence or absence of fluid hypotension is determined by repeating the lumbar puncture in the postoperative lethargic patient. When it occurs, postoperative intracranial hypotension usually appears within a few days after the surgical procedure, although its onset months after operation has been reported.[25] The development of intracranial hypotension in a 15-year-old girl after the Torkildsen procedure for obstructive hydrocephalus was described by Page.[11] The early postoperative course was uneventful until the third day, when she had headache and became drowsy. Lumbar puncture demonstrated a pressure of 60 mm. of water. Treatment with intravenous hypotonic saline and distilled water proved beneficial; within twenty-four hours, improvement appeared. The importance of early recognition of this complication of intracranial surgery is apparent since postoperative hypotension is a remediable process.

Chorobski[20] mentioned 6 cases in which fluid hypotensive syndromes appeared after cranial surgery. In one instance, a right temporal meningioma had been removed; 2 others had frontal lobe astrocytomas, another had a parietal meningioma excised, a fifth was operated upon for a parietal cyst, and the last had had evacuation of subdural and extradural hematomas. This author also gave extensive case reports of 3 other patients who had postoperative intracranial hypotension. Chorobski[20] suggested that low spinal fluid pressure appearing in the postoperative period results from disturbed formation of cerebrospinal fluid at the choroid plexus. That this was not secondary to a decreased systemic blood pressure was evidenced by normal blood pressure readings in his patients. He assumed further that certain metabolites from injured tissue, plus anoxemic areas of damaged brain, might result in nerve impulses that would decrease the cerebral blood flow. In addition to local alterations in nervous system activity at the site of operation, more remote areas, such as the hypothalamus, were believed affected by anoxemia. Chorobski's view was that this effect on the hypothalamus could explain the alteration in consciousness seen in some cases of postoperative intracranial hypotension as well as bring about decreased cerebrospinal fluid formation.

Shenkin[26] studied 3 patients who did not respond as expected after evacuation of subdural hematomas. All 3 were found to have marked intracranial hypotension as determined by lumbar puncture postoperatively. Cerebral blood flow determinations were performed on these patients by the nitrous oxide technic described by Kety and Schmidt.[27] The cerebral blood flow in these individuals with decreased spinal fluid pressure was found to be dimin-

ished, and the oxygen consumption was reduced. The cerebrovascular resistance was elevated and seemed to correlate with the reduction in cerebral blood flow. Shenkin assumed that the increased cerebrovascular resistance was the result of vascular spasm. The inciting factor producing vasoconstriction was not clear to him. This astute investigative study by Shenkin permits interpretation of the difference in clinical findings in spontaneous as opposed to postoperative and posttraumatic intracranial hypotension. The latter 2 types are apparently associated with decreased cerebral blood flow and, thus, alterations in responsiveness, marked apathy, and even coma are frequent manifestations. The level of awareness and responsiveness is usually much less affected in spontaneously occurring intracranial hypotension. As mentioned above, the etiology of vascular spasm in certain operative cases is not established. The resultant reduction in total cerebral blood flow may account for the diminished cerebrospinal fluid formation. Recent studies [28–30] have indicated that alterations in cerebral blood flow have a profound effect on cerebrospinal fluid pressure. Rich, Scheinberg, and Belle[29] have provided evidence indicating that factors which decrease the cerebral blood flow also decrease the spinal fluid pressure, while those that increase the cerebral blood flow will increase the pressure.

Posttraumatic intracranial hypotension. Leriche[31] in 1920 first described a syndrome associated with decreased spinal fluid pressure after head injuries. The initial report included a patient who sustained basilar skull fracture in a car accident. Spinal fluid hypotension was noted four days after the trauma and was associated with severe frontal headaches, nausea, and vertigo. Leriche[32] further reviewed the problem in 1931, and, subsequently, other reports[11,14,33] dealing with posttraumatic intracranial hypotension appeared. The frequently observed occurrence of decreased spinal fluid pressure with subdural hematoma was exemplified by Page's[11] patient, who had hematoma after a mild blow to the head. Two weeks after the injury, an opening pressure of 30 mm. of water was recorded on lumbar puncture. After the subdural blood had been removed, it was noted that the brain had fallen away from the dura on both the right and left sides. It is difficult to reconcile low pressure in the presence of an intracranial mass such as subdural hematoma. It has been proposed[19] that, in certain cases in elderly people, subdural bleeding may be the result rather than the cause of intracranial hypotension. Reduced intracranial pressure may be compensated for by abnormal engorgement of the cerebrovascular network. Also, as the brain tends to fall away from the dura, the dilated veins become stretched and relatively mild trauma may cause their disruption and subsequent hemorrhage.

The origin of intracranial hypotension after cranial trauma has been felt to be similar to that occurring postoperatively. In either situation, marked reduction in the state of awareness is often seen. Thus, it is suggested that factors affecting the cerebral blood flow may be important in the posttraumatic type as well as in hypotension occurring after cranial surgery.

Intracranial hypotension after lumbar puncture and with nerve sleeve tear. Certainly the most common disturbance associated with low spinal fluid presure is that following lumbar puncture. One usually encounters little difficulty in recognizing the syndrome of postural aggravation of headache that characterizes the postspinal puncture state. That the headache in this condition is related to intracranial hypotension is now generally accepted. The explanation of the reduced pressure, however, has stimulated many experimental studies and may not be completely answered to date.

It was pointed out by Dana[34] that the phenomenon of hypotension after lumbar puncture was most commonly seen in young persons and in those in whom the spinal fluid examination was normal. The same author suggested that the procedure in itself inhibits the secretory activity of the choroid plexus and thus decreases spinal fluid formation. The concept of leakage of fluid[35–37] through a tear in the dura secondary to lumbar puncture has been held responsible for many postspinal puncture headaches, especially those of short duration. Ingvar,[35] in 1923, performed experiments that demonstrated the importance of leakage of fluid after lumbar puncture. Methylene blue in saline was allowed to run into the ventricles of 4 cadavers. In 2 of the cadavers,

lumbar puncture was done before the ventricular infusions were given. Subsequent examinations showed the presence of blue-stained fluid in the lumbar epidural space of the 2 in which lumbar puncture had been performed. However, no such fluid was recovered in the other 2 specimens. Further evidence of the leakage theory was provided by Baruch's[38] studies in which indigo carmine injected into the spinal fluid appeared in the urine eight minutes after injection when the needle was withdrawn but not until sixty-three minutes when the needle was left in place in the spinal canal. The persistent nature of the dural tear was demonstrated by Leriche's[39] observation at laminectomy that a hole in the dura still existed several days after lumbar puncture had been done.

Whether leakage of fluid through a dural tear is the only mechanism of spinal fluid hypotension after lumbar puncture might be questioned. Occasional instances will appear in which symptoms of hypotension will persist for periods of time longer than can be explained readily on this basis. Schaltenbrand[19] has mentioned the possibility of alteration of choroid plexus function secondary to rapid removal of fluid at lumbar puncture. Indeed, vasomotor alterations in plexus function with diminution or cessation of secretion of cerebrospinal fluid might rationally explain those cases of persistent, severe headache after spinal puncture.

Intracranial hypotension after lumbar nerve sleeve tear has been described by Nosik.[40] His report was of a patient who fell backwards and landed on his buttocks. Characteristic hypotensive headache appeared shortly thereafter, and lumbar puncture showed an opening pressure of 50 mm. of water. Cases 1 and 2 of our series are believed to be examples of intracranial hypotensive syndromes of the same etiology. In both cases, onset of illness was marked by a fall on the buttocks with headache developing two days later. It can only be suspected that these 2 cases were associated with nerve sleeve tear and subsequent loss of spinal fluid by leakage. The similarity of these 2 cases to that of Nosik[40] is suggestive. Whether the diminished quantity of cerebrospinal fluid in such cases can be attributed entirely to leakage may again be questioned.

Intracranial hypotension associated with other medical conditions. Cerebral arteriosclerosis with reduced cerebral blood flow may be associated with intracranial hypotension. Shenkin and associates[41] have shown that arteriosclerosis associated with hypertension may result in a reduction of total blood flow to the brain. Shenkin and Finneson[12] encountered 11 patients with low spinal fluid pressures believed secondary to cerebrovascular disturbances. Mental obtundity was so marked in these patients that they were initially suspected of having brain tumor. Dehydration has been mentioned[40] as a causative factor of intracranial hypotension as well as uremia and severe systemic infections.[30] A single case has been reported[12] of decreased spinal fluid pressure in a patient subsequently found to have chronic barbiturate intoxication.

COMMENT

Most, if not all, of the above described disorders must be considered at least in part related to choroid plexus function. Formation of cerebrospinal fluid by a secretory mechanism as originally described by Flexner[42] requires an active process, with energy expenditure involving the epithelial cells of the plexus. Certainly, the elevated concentration of sodium, chloride, and magnesium ions in the cerebrospinal fluid as compared to those in the blood plasma cannot be explained by a process of ultrafiltration or dialysis. Regulation of such a complex process as cerebrospinal fluid secretion must involve several factors, including neural and humoral. One might propose a hypothalamic–posterior pituitary influence on cerebrospinal fluid formation in view of the knowledge of general body fluid and electrolyte metabolism. The abundant neural innervation of the choroid plexus suggests that vasomotor factors are probably important. Cerebral blood flow and even vitamin metabolism must be considered as factors bearing influence on a continued balance between formation and absorption of the cerebrospinal fluid. Thus, it is apparent that a variety of means exist by which disruption of choroid plexus function may result in the syndromes described above.

The relative frequency of occurrence of the various forms of intracranial hypotension is not known. However, hypotension following diag-

nostic lumbar puncture is certainly the most common. Low spinal fluid pressure with cerebral arteriosclerosis is believed to occur frequently, while postoperative and posttraumatic intracranial hypotension is seen less often. The spontaneous occurrence of intracranial hypotension is probably unusual. The prognosis of intracranial hypotension depends entirely upon the cause, the presence or absence of other brain disease, and the availability and utilization of proper therapeutic measures. Review of the literature and evaluation of our 3 cases described above suggest that the outcome in spontaneous intracranial hypotension is favorable and that complete recovery may be expected. Those causes of intracranial hypotension associated with cranial trauma and operative procedures do not ordinarily represent a serious threat if they are recognized and treated. In these situations, the underlying damage to the brain is the determining factor. Likewise, the low spinal fluid pressure syndrome occurring with cerebrovascular insufficiency is a secondary phenomenon, and the patient's outcome again depends on other factors.

Any discussion of the physiologic and pathologic derangement must also take into account the not too infrequent low pressure recording found on routine spinal puncture in patients without these symptoms. There must be a factor of individual variation as to what level of pressure produces symptoms. It is also possible that the absolute value of the pressure reading is only part of the picture and that the rate at which the spinal pressure fell is also a factor. It is possible that vascular and other mechanisms may accommodate for the gradual decrease in pressure but that rapid alterations keep ahead of the homeostatic forces and the characteristic symptoms ensue.

TREATMENT

A variety of therapeutic approaches has been described for intracranial hypotension. The preferred treatment depends upon the type of hypotension with which one is dealing and the underlying factors that are responsible.

In all forms of intracranial hypotension, general measures such as bedrest and salicylates or codeine for pain are helpful. Except in the postoperative period, elevation of the foot of the bed is recommended.

Spontaneous intracranial hypotension has been treated with intravenous injections of 20 to 40 cc. of distilled water or hypotonic saline solution.[6,7] Intrathecal injection of saline or Ringer's solution has been helpful,[7,19] as well as pilocarpine or papaverine hypodermically.[7] Experiments by Weed and McKibbon[43] in 1919 laid the groundwork for the use of intravenous water or hypotonic saline to increase cerebrospinal fluid pressure. Their studies on cats indicated that small doses of distilled water injected intravenously produced a prompt and enduring rise in the spinal fluid pressure. However, the use of hypotonic solutions must be regarded with caution because of the general effect on the electrolyte balance of the patient and the possible danger of hemolysis.

The problem one faces with posttraumatic or postoperative intracranial hypotension seems somewhat different in that reduction of cerebral blood flow with increased cerebral vascular resistance appears more important in pathogenesis. The cerebral vasodilating property of carbon dioxide inhalation has been used[12,26] to overcome the increased vascular resistance and thus to accelerate spinal fluid production. Subcutaneous saline was first suggested by Leriche[31] as a measure in posttraumatic intracranial hypotension. Therapeutic ventricular insufflation of air was advised by Vincent and associates[33] for these posttraumatic syndromes, and, later, lumbar air injection was used by Delay and Sizaret.[44] It must be recalled that spinal fluid hypotension appearing after cranial trauma not uncommonly occurs with a developing subdural hematoma. Correct diagnosis and immediate removal of the hematoma is of primary importance in this situation. The necessity of reinflating a collapsed cerebrum by intraventricular injection of saline or Ringer's solution after evacuation of a subdural hematoma or other cranial operations has been mentioned.[14,23]

Symptoms of intracranial hypotension after lumbar puncture usually abate spontaneously after a short period of time. Numerous methods have been used in attempts to shorten the duration of the illness. Posterior pituitary extract,[45] intrathecal saline,[36,46] and carbon dioxide inhalation[30] have all been described as having beneficial effects in hypotension after lumbar puncture. Recently, it has been sug-

gested[47] that the possibility of a hypotension syndrome may be lessened if the patient is kept prone for three hours after the lumbar puncture is performed.

For those cases of leakage of spinal fluid after a lumbar nerve sleeve tear, bedrest, again, is probably the most reliable method of treatment. Nosik[40] has stated that lumbar myelographic examination with its irritating effect on the meninges may promote healing. He also injected 1 cc. of the patient's blood into the lower spinal canal to induce an inflammatory response in the area.

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Neurology

BOOK REVIEWS

Pain and Itch, Nervous Mechanisms

Ciba Foundation Study Group No. 1. Edited by G. E. W. Wolstenholme and Maeve O'Connor, 120 pp., Little, Brown & Co., Boston, 1959. $2.50.

This small but highly informative volume, a published discussion of the first of the Ciba Foundation "Study Groups," is concerned primarily with information currently available on the electrophysiologic analysis of pain and the allied sensation, itch. The greater part of the discussion centers about the characteristics of electrical potentials of small peripheral fibers, delta fibers and, more especially, unmyelinated C fibers. The electrophysiologic behavior of nerve fibers of this order has only recently been accessible to analysis with the development of newer technics. Data and interpretations are given in a series of presentations by such leading investigators in the field as Prof. Zotterman, in whose honor the discussion was held, Prof. Wedell, J. M. Ritchie, and A. Iggo. G. Gordon speaks on patterns of activity in the central sensory pathway and S. Landgren on thalamic and cortical reception of afferent impulses from the tongue. In addition, there is a distinguished group of discussors, and the colloquium benefits by the chairmanship of Lord Adrian.

The discussion, as Lord Adrian points out, is only today's survey of where we stand in the physiologic analysis of pain and in the quest for the answer to specific energies of sensory modalities. For this reason and also because it contains much technical shoptalk, the book will be of greatest interest to specialists in the field, although there are two sections, one by Prof. W. B. Shelley dealing with local chemical factors in the itch stimulus in man and the other by Prof. Kugelberg containing observations in the pain of trigeminal neuralgia, which are of more direct interest to clinicians.

R. B. R.

Diseases of the Nervous System in Infancy, Childhood and Adolescence

by Frank Ford, 4th ed., 1,548 pp., Charles C Thomas, Springfield, Ill., 1959. $29.50

All neurologists should be indebted to Dr. Ford for the labor that he has put into this encyclopedic volume on pediatric neurology. Many new sections have been added to this edition. Old ones have been brought up to date. This is truly a reference book par excellence. Both neurologists and pediatricians will continue to refer to "Ford." In this edition, the section on examination has been omitted. It would seem to the reviewer that the section on neuroanatomy could well have been left out and a more detailed section on examination, with the standards of head size, growth, and so on, included. The bibliography is excellent, and the reader is frequently referred in the text to the most authoritative articles on the subject.

J.P.R.

Neurology of Infancy

by Anatole Dekaban, 388 pp., Williams & Wilkins Co., Baltimore, 1959. $12

This volume opens with the developmental anatomy and physiology of the nervous system from birth to 2 years of age. This section is particularly well done. It is practical and well illustrated, and one is able to correlate the development and myelinization of the nervous system with the child's functional development.

The methods of examination follow. Particularly useful are the levels of functional development that one can expect at various ages. The types of pathologic conditions that one can expect in an infant follow in logical sequence. There is a good balance between clinical description and pathologic findings.

A collection of conditions underlying cerebral palsy are described. It would seem to the reviewer that it would be better to put these in their proper place, such as congenital malformations and prenatal cerebral disorders, and do away with the vague term "cerebral palsy." A little more attention could have been paid to the hereditary disorders. This is an excellent book and will be very useful to anyone faced with the difficult problem of trying to evaluate the nervous system of the infant.

J.P.R.

Child Research in Psychopharmacology

organized and edited by Seymour Fisher, Ph.D., 216 pp., Charles C Thomas, Springfield, Ill., 1959. $6.50.

In spite of the ambiguous title, this compilation of papers presented in November 1958 at a closed meeting sponsored by the National Institute of Mental Health may have merit. The merit is found in the last chapter, which contains a list of 159 references on the effect of tranquilizing drugs in children. Some of these references are abstracted, and some degree of cross reference for drugs, types of study, and side actions is attempted. "Psychopharmacology is an area involving fundamentally four major disciplines: the organic chemist . . .; the psychologist . . .; the pharmacologist . . .; and the psychiatrist and clinical psychologist for eventual clinical evaluation" (Cole and Carr, p. 4). However, in spite of this definition, the meeting was attended by child psychiatrists who are not noted for their publications on the drug therapy of childhood behavioral or psychiatric disorders. Out of 22 guests, only 2 discussants and not a single participant appear in the 159 references as authors of original articles. No evidence is given in any of the reports that the participants had read any of the references or that they were familiar with or interested in drug therapy. The participants warn against indiscriminate drug therapy as a substitute for "proper care." This volume represents a negligible contribution to the problems of drug therapy of disturbed children.

C.C.P.

Right-Left Discrimination and Finger Localization: Development and Pathology

by Arthur L. Benton, 185 pp., Paul B. Hoeber, Inc., New York, 1959. $7.

This book begins with a historical review of the literature on the problem and gives a detailed account of methods of assessing right-left discrimination and finger localization.

Right-left discrimination begins to develop only in the early school years and reaches approximately adult level at age 12. Developmental disturbance of right-left discrimination occurs in children with mental deficiency, brain damage, and reading disability and, occasionally, in children and adults who otherwise seem normal. There is less information available concerning finger localization, but the acquisition and developmental disturbances of the skill seem to follow generally the same pattern as does right-left localization.

Acquired impairment of right-left discrimination and finger localization may occur in varying severity, may be unilateral or bilateral, may occur singly or together, and may occur in relative isolation or with other defects. Frequent concomitants of right-left disorientation and finger agnosia include mental deterioration in varying severity, aphasia, autotopagnosia, dysgraphia, dyscalculia, dyslexia, visual and spatial disorientation, color agnosia, and indifference to pain.

Neuropathologic and neuropsychologic con-

cepts of the determinants of disorders of finger localization and right-left discrimination are discussed.

This book is clear and well-written and stays within the bounds of the evidence. The author is to be commended.

J.R.B.

Progress in Neurobiology: IV.
The Biology of Myelin

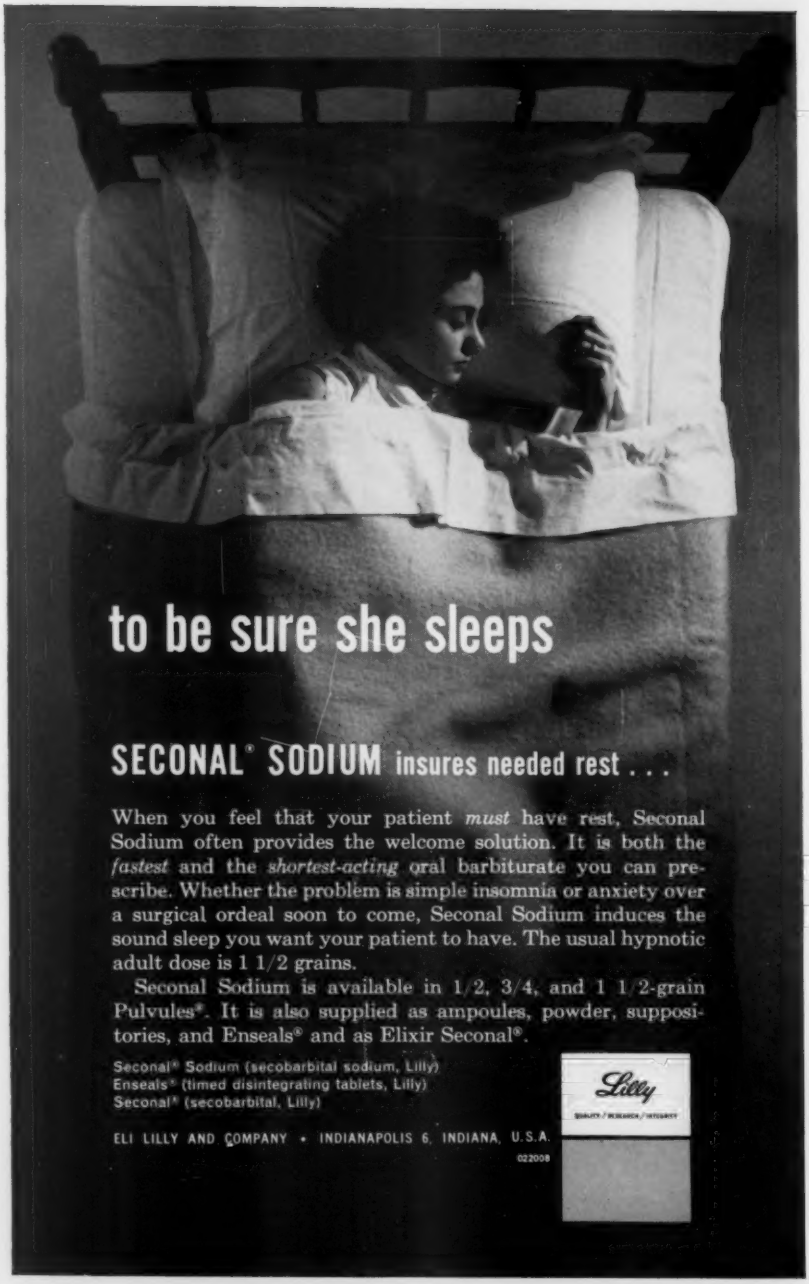
edited by Saul R. Korey, 405 pp., ill., Hoeber-Harper, New York City, 1959. $9.50.

This volume is the fourth in the Progress in Neurobiology series begun in 1955 by Drs. Korey and Nurnberger. It encompasses the papers and discussions presented during a symposium on the biology of myelin held in June 1958. The title is well chosen, since the coverage of the subject is varied and extensive. The structure of the myelin sheath and other cellular membranes as deduced by electron microscopy and physicochemical methods comprise 3 chapters by F. O. Schmitt, K. R. Porter, and S. A. Luse, respectively; 2 interesting papers by P. J. Harman and S. Glucksohn-Waelsch introduce genetic aspects of myelinization and nervous system development. Myelination in tissue cultures of embryonic neural tissue is discussed by W. Hild and M. R. Murray. The chemistry of lipid biosynthesis and myelin during development of the nervous system is covered by the papers of J. Folch and associates and of M. L. Karnovsky and associates. Physiologic properties of myelin sheaths and nodes of Ranvier and aspects of myelin in nerve trunks are discussed by I. Tasaki and A. M. Shames, respectively.

In addition to the foregoing, there are sections by K. A. C. Elliott on glial metabolism including water and electrolytes; by R. J. Rossiter and J. F. Berry on metabolism of the Schwann cell; by H. Koenig on nucleic acid and protein turnover in white matter; by E. P. Kennedy on phospholipid synthesis; by H. Waelsch on fatty acid and cholesterol synthesis; and by M. Rapport on plasmalogen structure, as well as chapters on Wallerian degeneration by R. D. Terry and J. C. Harkin and on experimental allergic meningoencephalitis by R. M. Condie and R. A. Good.

The papers are extensively illustrated, and the discussions are lively and well worth reading, especially to discover additional points about which there is honest controversy or lack of clear data. The volume is well recommended to all in the neurologic sciences who will want to keep abreast of progress in this important and complex field of neurobiology.

D.B.T.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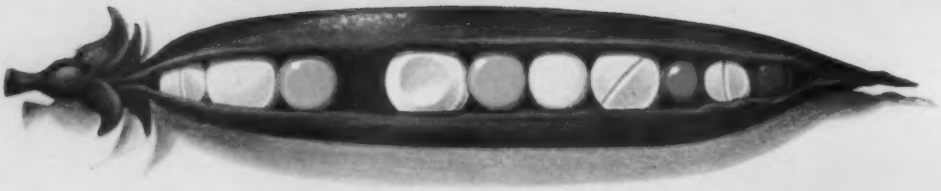

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1. Oswald, W.J.: Int. Rec. Med. 172:743 (Dec.) 1959. 2. Ehrmantraut, W., et al.: Scientific Exhibit, District of Columbia Medical Society (Nov. 24) 1958, Washington, D.C.

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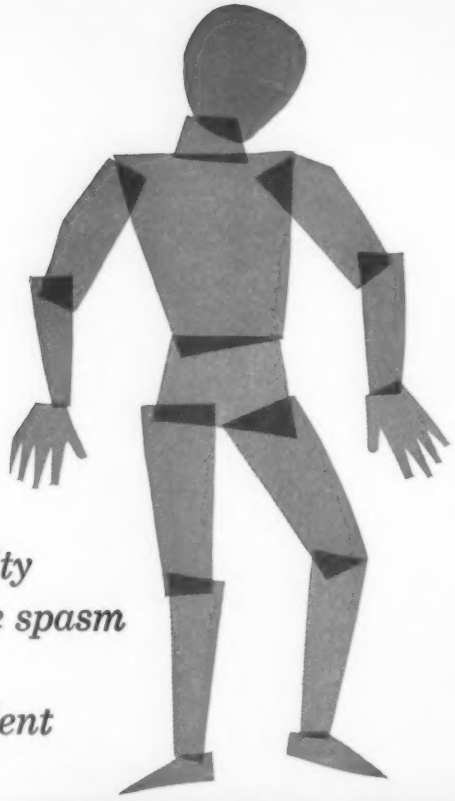

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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:87 (May 2) 1959.

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NEWSLETTER

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MAY 1960

Queen Square To Honor Centenary in London From June 20 to 25, The National Hospital, Queen Square, London, will celebrate its Centenary. After the Hospital Chapel Service Sunday evening, June 19, the program will be officially opened Monday morning (June 20) by the Right Honorable Derek-Walker Smith. That afternoon, there will be lectures: "The National Hospital and the Growth of Neurology" (Pearce Bailey); "C. H. Beevor -- The First Dean of the Medical School" (M. Kremer); "C. B. Radcliffe and His Contributions to Neurology" (S. P. Meadows); "Brown-Sequard and His Associations with the Beginnings of The National Hospital" (William Gooddy); and "The Role of The National Hospital in Russian Neuropathology" (I. S. Grashchenkov). The Monday program will close with clinical and other demonstrations in the afternoon .... On Tuesday morning (June 21), there will be presentations on "Past and Future Research in Poliomyelitis" (J. Marshall) and on "The Growth of Neuroradiology" (Hugh Davies). That afternoon, the lectures will include "Recollections of Queen Square" (Th. Alajouanine); "Sir Charles Ballance and His Work" (T. Cawthorne); "Bastian and His Contributions" (J. H. Paterson); "Elihu Yale in London" (J. F. Fulton); and the "Electrographic Diagnosis of Chronic Cerebral Circulatory Insufficiency" (H. Gastaut).... On Wednesday morning (June 22), the lecture program will include dissertations on the role of "The National Hospital and the Development of Neuropathology" (W. Blackwood); "...of Neurochemistry" (J. N. Cumings); and "The Early Neuro-ophthalmologists" (T. K. Lyle). In addition, there will be presentations on "Hughlings Jackson and Focal Epilepsy" (Chorobski); "Epilepsy and The National Hospital" (Denis Williams); and "Case Notes of The National Hospital for the Paralyzed and Epileptic Before 1900" (R. Hunter and L. J. Hurwitz). The Wednesday morning sessions will end with a paper on "Changes in Neurosurgery" by Mr. Harvey Jackson.

Panel Discussion on Neurology's Future Thursday morning (June 23) will highlight a panel discussion on the "Future of Neurology" (Pearce Bailey, presiding), which will be conducted in the Great Hall of the British Medical Association. The participants will be distinguished representatives of neurology, neurosurgery, psychiatry, internal medicine, and some of the basic neurologic disciplines.... Thursday afternoon, Sir Charles Symonds will give the Gowers Memorial Lecture on "Disease of Mind and Disorder of Brain."... Friday morning (June 24), the Victor Horsley Lecture will be given by Professor Norman Dott on "Brain, Movement and Time."

Critchley To Give Centennial Oration A feature of the program is the Centennial Oration to be delivered by Macdonald Critchley, Wednesday afternoon (June 22) at 4:30 p.m. at County Hall, S. E. 1. His topic will be "Jacksonian Ideas and the Future, with Special Reference to Aphasia." Earlier the same afternoon, the student nurses of the Postgraduate Nursing School will present a survey on neurologic nursing.

Daily Social Events To Follow Sessions A lively schedule of social events will complement the scientific sessions. On Monday, a cocktail party will be held at the Royal College of Surgeons and, on Tuesday, a reception, also at the Royal College of Surgeons and with a visit of the Duke of Edinborough. On Wednesday, a reception will be given by the London County Council at County Hall (5:30 to 7 p.m.), followed by the Centenary Subscription Dinner (informal dress, 7 p.m.). On Thursday (6 p.m.), the Institute of Neurology will give a wine and cheese party in Queen Square Garden.... On Friday evening, there will be a banquet (by invitation) at the Mansion House by the kind permission of the Right Honorable The Lord Mayor of London.

Neurosurgeons To Meet in Chicago The annual meeting of the Congress of Neurosurgical Surgeons will be held at the Palmer House, Chicago, October 26 through 30, 1960. The scientific sessions will center on problems of the spinal cord and nerve roots. A half day (October 26) postgraduate course in neurootology will be given by Dr. John R. Lindsay. The honored guest at the Congress will be Paul C. Bucy of Chicago. The Secretary-Treasurer to whom communications should be addressed is Dr. Richard L. de Saussure, Suite 101B-20 South Dudley Street, Memphis, Tenn.

Akert Receives Bing Award The Swiss Academy of Medical Sciences announced recently that Conrad Akert, University of Wisconsin Associate Professor of Anatomy, has been awarded the Robert Bing Award in Neurological Sciences. He will share the award, given for distinguished research, with Professor P. Buser of Paris. In June, Akert will deliver a lecture in Basel, Switzerland, and receive the award stipend of approximately $4,000. Dr. Akert's principal research interest concerns the hypothalamus.

Training Program in Neuroradiology Surgeon General Leroy E. Burney of the U. S. Public Health Service has announced the organization of a research training program in neuroradiology to be administered by the National Institute of Neurological Diseases and Blindness; 2 grants will be awarded to establish postgraduate training programs for the study of advanced neuroradiologic methods in the diagnosis and treatment of diseases of the nervous system. The training will be made available at the Albert Einstein College of Medicine and Columbia University's Neurological Institute. Both institutions will offer highly spe-

cialized training to qualified candidates wishing to pursue research careers in this field. The new program, to begin on July 1, will mark the opening of a new phase in the NINDB postgraduate research training programs. The training programs in neuroradiology are to consist of two years of intensive study. The first year of training will be devoted to neuroanatomy, neuropathology, neurosurgery, and clinical neurology. The second year will focus on advanced technics in neuroradiology.... NINDB is seeking other training centers where similar courses may be developed so as to relieve the acute shortage of competently trained neuroradiologists qualified to carry on research in neurologic and sensory disorders.

46 New Members Added Since 1959 Directory Since the publication of the 1959 AAN Directory of Membership, 46 neurologists and neurologic scientists have been added to the roster. Of the new members, 30 are juniors and 15 associates and 1 is an active member. The new members in all membership categories are Barron, R. (New Orleans); Brown, C. (Charter Oak, Calif.); Buchanan, D. (Washington, D.C.); Carnecchia, B. (West Chester, Pa.); Cohen, N. (San Francisco); de la Torre, R. (Skokie, Ill.); Doniger, D. (New York); Dreifuss, F. (Charlottesville, Va.); Egana, E. (Santiago, Chile); Eidelberg, E. (Long Beach, Calif.); Fine, D. (New York); Frenkel, M. (Chicago); Gabriel, A. (New York); Giord, N. (Quebec, Canada); Granger, D. (Hamden, Conn.); Greenbaum, P. (Tucson, Ariz.); Griggs, K. (Washington, D.C.); Hardin, W. (Ann Arbor, Mich.); Hernández-Peón, R. (Mexico); Isom, J. (Nashville); Jarcho, L. (Salt Lake City); Jenkins, T. (East Lansing, Mich.); Keeler, W. (Toronto, Canada); Kelley, J. (Washington, D.C.); Klein, L. (Durham, N. C.); Lane, M. (Bethesda, Md.); Levine, P. (Miami); Markovich, S. (Miami); McQuillen, M. (Washington, D.C.); Milligan, J. (Washington, D.C.); Moore, R. (Chicago); Pearson, C. (Los Angeles); Peison, W. (New York); Rubio, F. (New York); Sawyer, G. (Minneapolis); Seipel, J. (Washington, D.C.); Stornelli, S. (Long Beach, Calif.); Torres, F. (Minneapolis); Vergara-Garcia, I. (New York); Watkins, M. (Dallas); Weinstein, S. (Bronx, N. Y.); Whaley, R. (Washington, D.C.); Whitten, C. (Youngstown, Ohio.); Wolfgram, F. (Los Angeles); Woolsey, R. (Ann Arbor, Mich.); Ziziemsky, D. (LaPlata, Argentina).... During this period, 15 members also were graduated from junior membership to active membership, 4 from junior membership to associate membership, and 7 from associate to active.

Neurologic-Neurosurgical Symposium To Be Held in Lisbon The Santa Maria University Hospital of Lisbon (Hospital Escolar de Lisboa) will be the scene of an international neurologic-neurosurgical symposium October 21 through 23, 1960. The theme to be considered is "Principles of Nervous System Organization and Localization in the Light of Recent Neurological and Neurosurgical Knowledge." The program directors are Professors Georges Schaltenbrand (Wurtzburg) and Almeida Lima, who heads the

"Centro de Estudos Egas Moniz" at the University Hospital. The scientific program will consist of reports and related discussions by international authorities. The official languages are English, French, and German. Besides the scientific sessions, the conferees are invited to a symposium luncheon (Friday, October 21) as guests of Professor Lima and to a dinner offered by the Gulbenkian Foundation (Fundação Calouste Gulbenkian) on the evening of the same day. The social program also includes a drive to the environs of Lisbon on Saturday, October 22. The symposium is being sponsored by the "Centro de Estudos Egas Moniz" and the World Federation of Neurology. It is a fitting occasion to honor the memory of Professor Egas Moniz (1874-1956), Nobel Laureate, 1959, in Medicine and Physiology who pioneered frontal lobotomy and cerebral angiography. ... Before the symposium on Thursday, October 20, there will be the inaugural meeting of the WFN Commission (groupe de travail) of Neurological Surgery, which will be held in conjunction with representatives from the World Federation of Neurosurgical Societies.

Briefs On March 27, 1960, the First International Symposium on Parkinson's Disease was held at Columbia University's Arden House in Harriman, N. Y. Organized by William Black, President of the Parkinson's Disease Foundation, it was sponsored by the Foundation in collaboration with the National Institute of Neurological Diseases and Blindness. Participants came from the United States, Canada, Britain, Norway, and West Germany. H. Houston Merritt presided at the clinical sessions.... The Fourth Annual Meeting of the American EEG Society will be held at the Belmont Hotel in West Harwich on Cape Cod. Besides the regular program, there will be special symposia on epilepsy and the medicolegal aspects of electroencephalography.... A three-day International Meeting of Electromyographers will be conducted by Professor F. Thiebaut and Dr. F. Isch in the Neurological Department of the Faculty of Medicine of Strasbourg October 17 through 20, 1960. At the end of the scientific sessions, program participants may enroll for a one-week practical course in electromyography. Further information may be obtained from Dr. F. Isch, Laboratoire d'Electromyographie, Clinique Neurologique, Hospices Civils, Strasbourg, France.... Roland P. Mackay was elected Chairman and H. Houston Merritt reelected Vice-Chairman of the Medical Advisory Board of the National Multiple Sclerosis Society. Mackay succeeds Augustus S. Rose as Board Chairman. Merritt is also President of the Society's International Panel on Multiple Sclerosis and Chairman of its Fellowship Committee and has been a member of its Medical Advisory Board since 1948.

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References: 1. Schwab, R. S.: Geriatrics 14:545 (Sept.) 1959. 2. England, A. C. and Schwab, R. S.: A.M.A. Int. Med. 104:439 (Sept.) 1959. 3. Schwab, R. S. and England, A. C.: J. Chron. Dis. 8:488 (Oct.) 1958. 4. Glaser, G. H.: Connecticut M. J.: 23:390 (June) 1959. 5. Doshay, L. J. et al.: J.A.M.A. 160:348 (Feb.) 1956. 6. Doshay, L. J. and Constable, K.: J.A.M.A. 170:37 (May) 1959.

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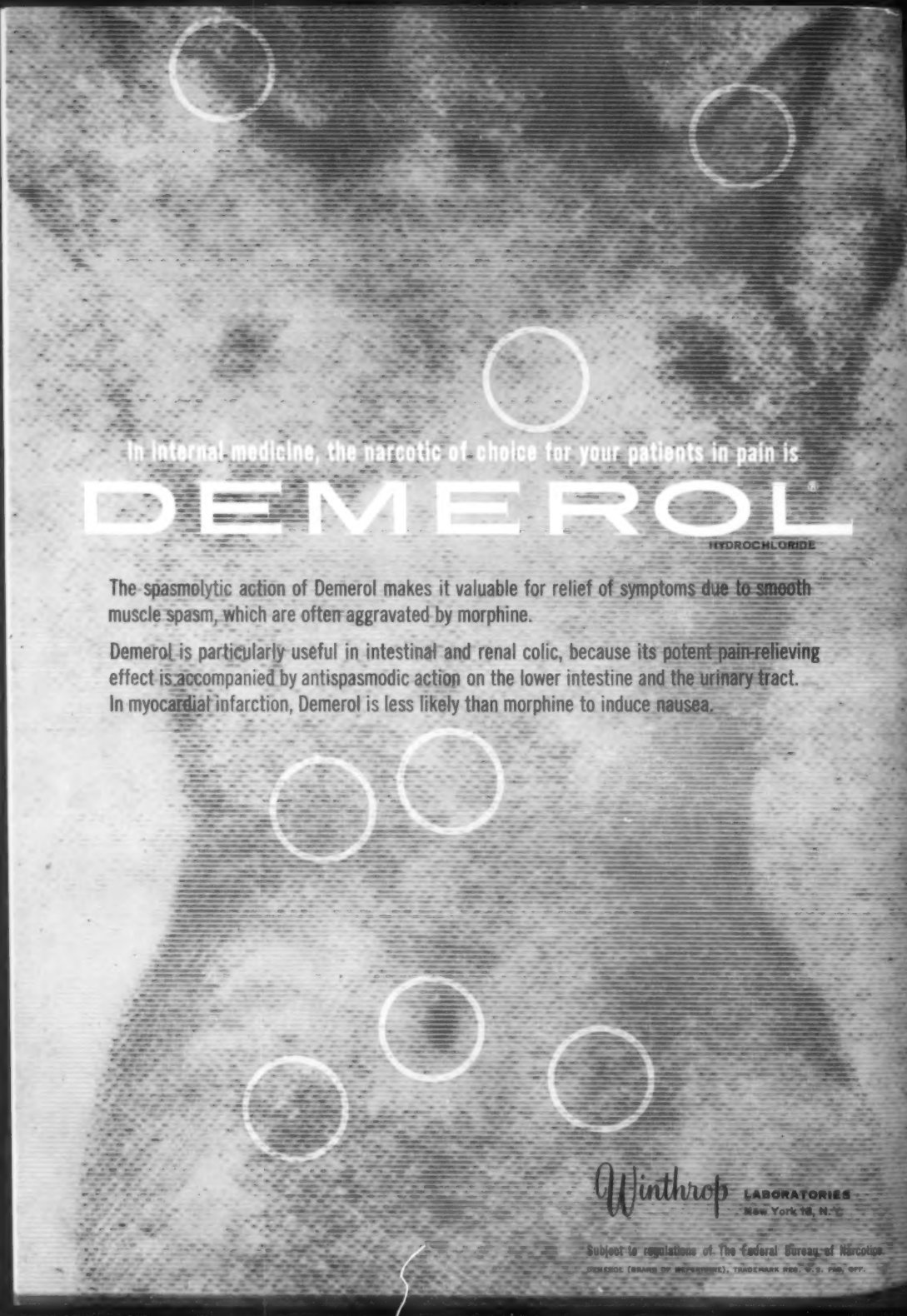
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